Daughton, C.G. "Pharmaceuticals in the Environment: Sources and Their Management," Chapter 1, 1-58, *In* Analysis, Fate and Removal of Pharmaceuticals in the Water Cycle (M. Petrovic and D. Barcelo, Eds.), *Wilson & Wilson's Comprehensive Analytical Chemistry* series (D. Barcelo, Ed.), Volume 50, Elsevier Science; 2007, 564pp.

Chapter 1. Pharmaceuticals in the Environment: Sources and Their Management

by Christian Daughton
Environmental Chemistry Branch, Environmental Sciences Division, National Exposure Research Laboratory, U.S. EPA, 944 East Harmon Avenue, Las Vegas, NV 89119, USA; Tel.: 702-798-2207; fax: 702-798-2142; E-mail address: daughton.christian@epa.gov

1.1 Pharmaceuticals in the Environment: Sources and Their Management

INTRODUCTION

An issue that began to receive more attention by environmental scientists in the late 1990s was the conveyance of pharmaceuticals to the environment by way of their use in human and veterinary medical practices and personal care. Pharmaceuticals and personal care products (PPCPs) comprise a remarkably diverse array of thousands of unique chemical substances, most of which are purchased for use directly by, or for, consumers and medical and agricultural practices. Of the so-called "emerging" pollutants, PPCPs perhaps serve as the prototypical examples because they amply illustrate the many dimensions and new questions associated with non-regulated pollutants. Of the many aspects that set them apart from conventional pollutants, a defining one is their diffuse, dispersed origins from the combined and varied actions, behaviors, and activities of multitudes of individuals. At the same time, many of these compounds experience significant parallel uses in agriculture. As consumer items, the minuscule contributions from each individual, while meaningless by themselves, combine to yield measurable environmental residues. Although pollutants from dispersed sources and origins are not fully amenable to engineered solutions for controlling their entry to the environment, the potential for significant reductions is possible through comprehensive environmental stewardship strategies such as pollution prevention.

Of the many aspects of PPCPs as environmental contaminants, this chapter focuses only on two – sources and their management. Numerous sources and pathways serve to convey PPCPs to the environment after their use by humans and in animals. Some have origins from both natural and anthropogenic sources. After all, the design of many synthetic drugs was patterned or inspired from naturally occurring substances that possess extraordinary pharmacologic activity. Careful consideration of these sources can help guide the development of strategies for reducing or minimizing the introduction of PPCPs to the environment. These strategies include a wide spectrum of possibilities that span drug design, commercial distribution, end usage, disposal, and treatment for waste and drinking water. The last mentioned approach — treatment technologies — is the subject of other chapters. This chapter's focus is on the pollution prevention aspects of environmental stewardship; for a general discussion of the principals of environmental stewardship, see EPA (2005). An important perspective to keep in mind regarding pollution prevention relates to the many unknowns regarding the significance of PPCPs in the environment — why should effort be devoted to reducing the disposition of PPCPs to the environment if the potential for adverse effects on the environment or humans is largely unknown. The answer resides partly in the precautionary principal (e.g., see: Harremoës et al. 2001) and partly in the fact that other, unanticipated benefits can derive from implementing the principals of environmental stewardship. These collateral benefits could include improvement of health care effectiveness, reduction in health care costs, and reduction in human and animal accidental (and purposeful) poisonings — all potentially deriving directly from reduced usage rather than from reduced exposure to environmental residues.

Scope — The Universe of Pharmaceuticals

By itself, the word "pharmaceutical" refers to a chemical prepared or dispensed in pharmacies and which treats or prevents or alleviates the symptoms of disease or physiologic function. Technically, this limits the scope solely to prescription drugs. A narrow definition of "pharmaceutical" therefore excludes over-the-counter (OTC) drugs, diagnostics (e.g., x-ray contrast media, including certain radiologicals), nutritional and dietary supplements (ephedra is an example), illicit drugs, cosmetic or lifestyle drugs not essential for medical purposes, and the broad range of personal care product ingredients.

For the purposes of this chapter, however, the universe of chemicals encompassed in the scope of PPCPs will be defined to include all chemicals used for humans, domestic animals, or agricultural crops that: (i) treat disease, (ii) alter or improve physiological, cosmetic, or emotional function, appearance, or status, (iii) prevent disease (prophylaxis) or maintain health, (iv) help in the diagnosis or monitoring of health or disease, or (v) serve to formulate the active ingredient into a commercial product (e.g., excipients and delivery vehicles). The scope includes all preparations intended for topical, pulmonary, or parenteral (injection) administration or ingestion, as well as suppositories and enemas. The obvious galaxies of chemicals in this universe are the diverse arrays of human and veterinary prescription and OTC medications. But others include diagnostic agents (e.g., X-ray contrast media, radiopharmaceuticals), vaccines, and “nutraceuticals” (bioactive dietary supplements such as huperzine A and "functional foods) and food supplements (including vitamins). Drug consumption originates not just from approved usages, but also from unapproved (e.g., extra-label) and illegal usage. Illicit drugs, in particular, comprise an unknown but possibly significant fraction of total drug usage, and consequently contribute to individual environmental residues and to the overall environmental loading of PPCPs.

As nutraceuticals (alternative spelling "nutriceuticals") and functional foods become more sophisticated, the demarcation between these exclusively naturally derived substances (e.g., phytochemicals) and the predominantly synthetic pharmaceuticals will become less distinct. According to this delineation of scope, also included would be materials resulting from genetically modified organisms (GMOs) and other biotechnology products, as well as radiopharmaceuticals and nanoscale materials used in medicine. The scope includes both licit and illicit drugs. PPCPs comprise both anthropogenic and naturally occurring substances, derived from such sources as microorganisms (e.g., antibiotics and toxins), tissues, plants, animals, petroleum products, and nanoscale materials. Traditionally included in the scope of PPCPs from natural sources are the toxicologically important group of endogenously synthesized and excreted steroid hormones (e.g., the estrogens, androgens, progestagens, gluoco/mineralcorticoids, and thyroid hormones); these naturally produced substances are often included in the scope of PPCPs because their mechanisms or modes of action are so similar to their synthetic relatives ("artificial hormones" and "mimics") and because they are sometimes directly formulated as their unaltered or prodrug forms in medications (e.g., estradiol, testosterone). Of importance to note is that estrogenic and androgenic activity together with other forms of endocrine modulation (e.g., "endocrine disruption") in the environment can originate from both synthetic and natural sources, and only an unknown portion originates from PPCPs. Synthetic and endogenous relatives sharing the same mechanism or mode of action therefore jointly contribute to cumulative and aggregate exposures. Although the topic of endocrine disruption, especially with respect to the effects of sewage effluents on aquatic life, is far beyond the scope of this chapter, the major unknowns and complexities surrounding the subject are articulated by Sumpter and Johnson (2005).

For the purposes of this document, the universe of PPCPs includes not just the parent form of the chemicals (whether the active ingredients or prodrugs [a "prodrug" is an inactive precursor that is converted to the active form by normal metabolic processes; the fibrates are an example]), but also their bioactive metabolites and transformation products (including conjugates). Note that an intersection exists between pharmaceuticals and pesticides, where several are registered for both uses (lindane, triclosan,

and triclocarban are but three examples). Another intersection occurs with endocrine disrupting chemicals (EDCs) and PPCPs.

Some miscellaneous statistics supply ample perspective for the breadth and size of the pharmaceutical market. As of March 2005, the FDA lists in its Orange Book (FDA 2005a), whose updating frequency ranges from daily to monthly, over 11,000 distinct prescription drug formulations and dosages, comprising pharmaceutical equivalents, pharmaceutical alternatives, and therapeutic equivalents, as well as those that have been discontinued from marketing (FDA 2005b); it must be noted that these numbers are not distinct drug entities, which are a subset of the total numbers of drug preparations.

The number of drugs cataloged in 2005 from Germany and the EU (Rote Liste Service 2005) include roughly 9,000 preparations in over 11,000 different dosage forms and 35,000 products. The total number of medicinal preparations worldwide probably exceeds tens of thousands, 60,000 being a figure cited by Tropsha (2000). Each of these products is marketed for one or more of over 80 major therapeutic categories, but so-called off-label prescribing for non-approved conditions is also widespread. Of significance with respect to the occurrence of PPCP residues in the environment is that the relative usage rates for individual drugs can vary dramatically not just between countries (whose approved drugs are not necessarily the same), but also among geographic locales within a country, as a function of prescribing practices and preferences (Daughton 2003a). Many of the excipients used in drug formulation are also used in the processing of foods, but derivation of most excipient residues from drugs is probably minor compared with their sources from foods.

From 1999 to 2000, 44% of all Americans were taking at least one or two prescription drugs during a prior month, and nearly one in five were taking three or more. Nearly 84% of all Americans aged 65 and older were taking at least one or two prescription drugs, and nearly half were taking three or more. Other trends in increasing medical drug usage are presented in the report prepared by Department of Health and Human Services for Congress (HHS 2004).

The types of drugs most commonly prescribed or used, together with their usage rates, vary over time, as distinct therapeutic classes and their individual members change in popularity and as new active pharmaceutical ingredients (APIs or "drug substances") are introduced to commerce; an API is any chemical constituent having pharmacological activity or other useful effect in the diagnosis, cure, mitigation, treatment or prevention of disease, or that affects the structure or a function of the body. Types of drugs also vary with geographic locale (from country to country and even within adjacent regions) because of varying prescribing practices and customs, differing health needs, and continually evolving patient desires and expectations. The broad spectrum of the types of human pharmaceuticals (i.e., therapeutic categories, and drug classes and subdivisions) that are most frequently prescribed can be perused by referring to any "preferred drug list" (also known as a drug "formulary") maintained in the U.S. by the healthcare plan industry; example formularies, under Medicare, can be accessed for all U.S. states (see database maintained by Medicare 2006; a specific example selected at random can be seen at: EBRx 2006). Other countries have similar formularies (e.g., for Britain, see BNF 2005). Analogous formularies exist for veterinary medicine (e.g., see UM 2006). The most commonly prescribed individual drugs in each class or subdivision can be obtained from various pharmaceutical data providers; for example, the most frequently prescribed pharmaceuticals in the U.S. are compiled by NDCHealth (2005a). The publicly available list currently comprises the top 300 most frequently dispensed medications in the U.S. in 2004 (NDCHealth 2005a); each of these medications can be assigned to one or more therapeutic classes/subdivisions mentioned earlier. Those pharmaceuticals from each class that have been repeatedly identified in various monitoring studies are reported in various overviews (e.g., Daughton and Ternes 1999; Fent, Weston, and Caminada 2006).

A compilation of the top 200 prescriptions for 2004, according to U.S. sales, is also provided by NDCHealth (2005b). Worldwide sales in 2004 for the top selling 500 drugs were nearly $300US billion (Med Ad News 2005). Per capita sales in the US ($552) were nearly 40% higher than those of the next highest country, Japan (VFA 2005). Global audited sales of all pharmaceuticals reached $518US billion in 2004 (IMS Health 2005). Coincident with these measures of absolute consumption is the attendant annual growth in usage as reflected by annual sales and dispensing; for example, IMS Health (2006) reported U.S. prescription drug sales increased 5.4% from $238.9US billion in 2004 to $251.8US billion in 2005, generic sales increased nearly 21%, and dispensed prescriptions in the U.S. increased 4.7% over the same period. IMS Health predicts continued 5-year growth of 5-8%.

Although the number of existing drugs is quite large, the rate at which new drug entities are introduced to the U.S. is very small. For the 10-year period 1993-2003, the number of new molecular entities (NMEs) approved yearly by the U.S. FDA ranged from 9 to 35 (FDA 2005c); a NME is a medication whose active ingredient has never before been approved in the U.S. for marketing in any form. While thousands of distinct drug entities exist, and hundreds are used routinely throughout the world, roughly only 100 or so PPCPs have been routinely identified so far in various environmental samples. This discrepancy results largely from the fact that (1) not all drugs are used in quantities sufficient to be detected as environmental residues, (2) many drugs are either extensively metabolized, lessening the excretion of the parent chemical, or rapidly transformed by engineered or natural processes, and (3) not all pharmaceuticals are easily detectable at low concentrations in complex environmental matrices using current chemical analysis methodologies. But also important to keep in mind is that those drugs that have been detected in the environment have resulted from targeted monitoring; and therefore, those not targeted escape detection – just as with any unregulated pollutant (Daughton 2005). Many additional PPCPs undoubtedly occur as contaminants but they have yet to be targeted for monitoring. Surprisingly, a comprehensive compilation of all PPCPs reported in the literature as environmental contaminants does not yet exist in a publicly available database.

It is important to note that this very brief presentation of some facts regarding human drug use is pertinent neither to veterinary drugs (and those used in animal husbandry) nor to personal care products. Entirely different databases need to be consulted to glean this information. A major lesson is that information regarding drug usage (whether human or animal) is extremely difficult to obtain easily or without cost. Subscription services are required for accessing human prescription drug usage (e.g., see references cited by Daughton 2003a). It is also important to recognize that prescription drugs represent but a small portion of overall drug usage compared with OTC drug sales. Illicit drugs and those obtained on the black market represent additional major origins for drugs (Daughton 2001), but their contribution to overall residues in the environment is unknown, with investigations just beginning (e.g., Zucatto et al. 2005; also see news article by Turque 2006).

Without access to proprietary data, it is difficult if not impossible to gain a sound perspective regarding the total numbers and quantities of distinct drug entities used in the U.S., if not worldwide. This has major ramifications with regard to assessing those PPCPs that might play the most important roles as environmental pollutants. Information concerning the PPCPs that are in use commercially, coupled with their quantities (active ingredients), comprise one of several factors that determine the types and quantities of the parent chemical and transformation products that can eventually become pollutants as a result of their intended end use. Neither total numbers of distinct chemicals in use as PPCPs, nor their sales data, nor prescription data are by themselves useful for even predicting the potential occurrence of these chemicals in the environment. Even more data are required for predicting the flux of distinct entities (including parent drugs and transformation products, sometimes referred to as "degradates") to the environment.

Regardless, this brief sketch of the commercial significance of pharmaceuticals provides the backdrop reflecting the extent of widespread usage of pharmaceuticals, at least in Western countries, and superficially explains the ubiquitous occurrence of at least trace residues of these consumer products in certain environmental compartments. With this discussion aside, it is also critical to keep in mind that the absolute quantities of individual PPCP residues is only one factor required in assessing their significance in the environment. Other key attributes include biological potency. A simple example would compare the overall significance of a weakly estrogenic xenobiotic (e.g., nonylphenol, a breakdown product of the ubiquitous nonylphenolethoxylate surfactants) with a potent estrogenic drug (e.g., ethynylestradiol). The former is manufactured and introduced to the environment in quantities orders of magnitude greater than the latter, but their relative potencies, which also differ by many orders of magnitude, serve to place them on comparative footings with regard to impacts in the environment.

Background Regarding the Acronym "PPCPs"

The acronym "PPCPs" was coined in a review article by Daughton and Ternes (1999). Its original intent was merely to serve as a shorthand in that article to refer to "Pharmaceuticals and Personal Care Products." The term was subsequently assimilated into the environmental science literature, presumably for convenience. This broad collection of substances includes any product consumed by individuals or domestic animals for any number of countless reasons pertinent to health, performance, cognitive and physical function, or appearance. Note that the similar, truncated acronym "PCPs" is sometimes used when reference is made solely to "personal care products," exclusive of pharmaceuticals. This sometimes creates confusion if PPCPs and PCPs are interspersed frequently in the same discussion.

While the use of acronyms is often a bane of science — at best unnecessarily confusing or at worst an obfuscation to communication — acronyms are very useful when researching the published literature. This is especially true for the topic of "pharmaceuticals and personal care products" as environmental pollutants as none of these "key" words has any specific meaning useful for literature searches. Searching the literature relevant to pharmaceuticals and personal care products in the environment is made difficult because there are no search terms specific to the topic other than several rather unique acronyms, such as PPCPs. The words "drug," "pharmaceutical," "medicine," "medication," "medicament," "medicinal," "therapeutant," "diagnostic agent," "active ingredient," or "personal care product" are all much too broad by themselves, encompassing a vast literature, largely irrelevant to environmental science. General searches can be better focused, however, by coupling any combination of these terms (or names of specific PPCPs) with others that are used more specifically in the environmental literature but much less so in the traditional medical literature: "aquatic," "sewage," "sludge," "manure," "pollutant," "pollution," "contaminant," etc. Even though PPCPs as a pollution concern derive primarily from the practice of human and veterinary medicine, the topic has been rarely discussed in the medical literature itself (early instances first being Zucatto et al. 2000 and then Daughton 2002 but few since, e.g., Sherer 2006). Another way to better target literature searches when using subscription databases is to limit keyword searches to the environmental literature.

The advantage of a distinctive acronym is that it allows for more focused literature searches — providing results that are almost always directly relevant to the topic. But a proliferation of yet other acronyms adds to the already difficult task of performing targeted literature searches. In addition to the acronym "PPCPs," some other acronyms that have appeared in the literature include "PhACs" (Pharmaceutically Active Compounds), which was coined by Sedlak et al. (2000); sometimes the shorter acronym "PACs" is used in its place. While encompassing therapeutically active drugs, PhACs would not include non-therapeutic pharmaceuticals (e.g., diagnostic agents, X-ray contrast media being one example), nor would it include personal care products (such as synthetic musks or parabens). Yet another acronym appeared in 2003 — "PCPIs" (Personal Care Product Ingredients); PCPIs is analogous to PhACs (referring to the actual "active" ingredients), but specific for personal care products (Pedersen et al.

2003). The term "PhPCPs" has also been used recently. It is worth noting that both PhACs and PCPIs (both of which are subsets of PPCPs) exclude the so-called inert or "inactive" ingredients used in product formulation (e.g., excipients); but even the "inert" ingredients can have biological effects (examples include alkylphenolic surfactants, parabens, and phthalate esters, used in various personal care products) or alter the absorption or metabolism of the API; the role of "inert ingredients" might become more significant as nanomaterials become more widely used in medicine. Another expression that aptly captures the pollution aspect of PPCPs is "feral pharmaceuticals," a term coined by Fisher and Borland (2003).

An Historical Perspective Regarding the Published Literature and PPCPs

The annual rate of published articles directly relevant to PPCPs has grown exponentially since the mid-1990s. The published English literature had been rather scarce up until the mid-1990s. An informal assessment of one compilation of the published literature (Daughton/EPA 2005) reveals that by 1998, the yearly publication rate was merely several dozen. In 2000, the yearly rate multiplied but was still less than 100. Beginning in 2001 and continuing through 2003, the yearly rate climbed past 100, and in 2004 it exceeded 200. As of 2005, it has become increasingly difficult to locate and digest all of the citations that are relevant to PPCPs because the breadth of journals covering the issue has greatly expanded, because these journals often carry multiple PPCP articles in each issue, and because the number of topics encompassed by the field continues to grow.

Discussions of the environmental ramifications of PPCPs originally focused on their occurrence and monitoring, primarily in surface/ground waters and untreated/treated sewage. This work was driven primarily by environmental analytical chemists, as new instrument technologies expanded the types of unknowns that could be easily identified, as instrument sensitivity increased, and as detection limits of analytical methods were lowered. This focus continued until the late 1990s, when it began to expand to waste treatment and fate/transport. In the last couple of years, more attention is beginning to be devoted to exotoxicology, pollution prevention, and environmental stewardship. Likewise, the scope of environmental compartments under investigation has expanded from primarily waters to now include sediments (and suspended particulates), sewage sludge (and biosolids), air (e.g., PPCPs sorbed to suspended particulates), and biota.

As the literature on the many aspects of PPCPs continues to grow, it is only possible to cite a select few articles that cover some of the facets summarized in this chapter. The vast majority of pertinent references must necessarily be omitted because there are simply too many; this is not to be interpreted in any way as a reflection of the quality of these many works. But by referring to the literature cited in a limited number of key articles, the reader can readily gain access to a more expansive literature. Some useful articles that offer broad perspectives on either human or veterinary pharmaceuticals, especially regarding sources and origins, include: Boxall et al. (2004), Daughton and Jones-Lepp (2001), Daughton and Ternes (1999), Díaz-Cruz et al. (2003), Halling-Sørensen et al. (1998), Heberer (2002), Jorgensen and Halling-Sørensen (2000), Kolpin et al. (2002), Kümmerer (2001, 2004), Petrovic et al. (2005), and Ternes (2001).

1.1.1 Sources and pathways for pharmaceuticals to the environment

Importance of Understanding Sources and Origins

The following discussion of the sources and origins of PPCPs occurring as residues in the environment is necessary for gaining an appreciation of the scope and magnitude of the entire issue. An understanding of origins and sources is required so that knowledge gaps can be assessed and so that future research or

actions can be most effectively targeted. A key concern regarding sources is whether they lead to immediate or delayed, direct exposures of biota or humans without additional transport being required (e.g., via the trophic food chain); the recently discovered link between diclofenac-treated cattle and die-offs of scavenging vultures in Southeast Asia is but one example (Oaks et al. 2004). Thorough understanding of sources and origins is also essential for implementing not just engineered control measures, but also for designing effective pollution reduction measures, a topic that will be discussed in the second part of this chapter. A comprehensive inventory of the types of sources for each PPCP ingredient does not exist; such a system overlain with geographic information would be extremely useful.

Although the significance of pharmaceuticals as trace environmental pollutants in waterways, and on land to which treated sewage sludge or wastewater has been applied, is largely unknown, the fact that certain PPCPs with short environmental half-lives can nonetheless have continual persistence (noted by Daughton and Ternes, 1999, and later referred to as "pseudo-persistence" by Daughton 2002), because of their continual introduction via effluents from sewage treatment facilities and from septic systems, poses two immediate concerns. First, with respect to ecological integrity, the potential for adverse effects on biota is largely unknown, especially for aquatic life, and secondarily for those organisms that are part of the food chain involving sewage-amended land. Second, drug residues that make their way to drinking water sources could pose the potential for significant problems with regard to public acceptance of, and trust in, their water supplies. This second concern is not widely appreciated and results from the complex ways in which risk is perceived (Daughton 2004a). The overarching environmental concerns associated with PPCPs as pollutants have been summarized by Daughton (2003a); the potential for subtle effects, in contrast to overt acute effects, was identified as the primary concern by Daughton and Ternes (1999).

One of the major attributes that distinguishes PPCPs from other chemicals that become pollutants is the fact that they are primarily marketed as products for use by the public. As such, they do not fit into the conventional mold of pollutants that result from commercial activities, such as manufacturing, or from waste treatment practices (e.g., incineration). While most of these conventional sources of pollution are well-defined point sources, PPCPs instead emanate from the confluence of individually minuscule contributions from each of multitudes of individuals or animals. The private individual as polluter, as a result of direct use of chemicals for personal purposes, is only a recently recognized phenomenon. At the same time, it is important to recognize that PPCPs are not the only galaxy of chemicals that the public directly uses (or creates). Other galaxies contributing to pollution include household products used for cleaning and maintenance, wastes from electronics, fuel combustion, and even food; some of these, however, can also serve as sources for certain PPCPs (e.g., caffeine from foods, and broad-spectrum biocides such as triclosan and triclocarban, which are used in many consumer products). There is also an intersection between pharmaceuticals and pesticides, a small select number of which serve double duty as both registered pesticides and as PPCPs; some examples are presented later (see section "Multiple Aggregate Sources"). Many of the issues discussed here are relevant not just to PPCPs, but also to other unregulated pollutants, including the so-called "emerging" pollutants and chemical stressors in general (see discussions at: Daughton 2004b, 2005).

Drugs can enter the environment by a number of distinct and varied routes. The two general means by which they gain entry are indirectly (involuntarily) by excretion and bathing, and directly (purposefully) by disposal. Disposal of drugs that are no longer needed or wanted occurs by discarding to trash (which in turn usually goes to landfills) or by directly discarding to sewage systems (usually via the toilet). Although the long-accepted means of disposing to sewerage by flushing down toilets is now known to maximize the ability of a drug to enter the environment, the rationale behind this approach is to minimize the chances of consumption by others for whom the drug was not intended. Poisoning of adults and children by medications discarded by others is a problem of increasing concern to healthcare professionals. To date, however, there are no widely available alternative means, at least in the U.S., for

drug disposal that are inherently protective of human safety. Drug disposal is a deceivingly complex topic. The many issues and dimensions surrounding drug disposal (and other approaches to pollution reduction) were covered in a 2-part monograph (Daughton 2003a,b) and will be further addressed in the second part of this chapter.

It is also important to note that while most drugs enter the environment from individually dispersed sources, primarily via sewerage (much of which is recombined into flows leading to publicly owned treatment works — POTWs — which in turn yield point-source discharges into receiving waters), some sources are extremely localized (e.g., privately owned septic leach fields, straight piping, cemeteries, etc.); straight-piping is the practice where untreated, raw sewage is illegally discharged without treatment directly to the environment immediately from the point of origin, often private residences. Some origins therefore may have broad significance for the environment while others might have significance only in certain special, local circumstances.

SOURCES/ORIGINS

Before discussing sources and origins of PPCPs in the environment, we must recognize that such a discussion can get confusing without defining some rather arbitrary boundaries and artificial definitions. The distinction between source, origin, and fate is often vague. At any point along a pollutant's environmental transport chain, a variety of different exposure and effects scenarios can come into play. Any point in the chain can be considered to be a source (but not necessarily an origin). For example, sediments or edible plants become an environmental compartment in terms of transport and fate, but as a result, they also become a source in terms of being a reservoir for subsequent re-release (e.g., to another compartment such as water) or exposure (e.g., as food for humans or wildlife). "Sources" include routes to and from the end-user.

The topic of PPCPs as pollutants is intimately tied to a bewildering array of phenomena that transport and transform these chemicals from one place to another via a multitude of distinct "routes" by which the chemical is emitted, dispersed, or otherwise introduced to the next "compartment" or ultimately to a biological receptor. As an example, any point in the water "cycle" or in a waste treatment process chain can be considered a "source" for the downstream connecting points, which in turn then become sources themselves. What constitutes an actual "source" is often difficult to define as a PPCP leaves a manufacturer and progresses until it leaves the supply-consumption cycle and is released to the environment, where it can reside in any number of environmental compartments and exchange among them. If we limited our discussion to those "sources" that serve as the points where PPCPs leave the consumption cycle and enter the environment, the discussion would be rather simple. Any discussion of "sources" will therefore necessarily intermingle with discussions about fate and transport, which are covered in more detail in other chapters of this book. A hint of this complexity can be seen in Figure 1. So we will recognize from the outset that some overlap with other chapters will be inevitable but discussion of processes traditionally considered to constitute "fate and transport" will be minimized. This is perhaps made clearer by distinguishing "origin" (as the point at which something comes into existence) from "source" (as the point from which something is derived or obtained).

Anthropogenic pollutants gain entry to air, surface and ground waters, land, and biota as a result of manufacturing emissions, power generation, waste disposal (e.g., incineration, landfills), accidental releases (e.g., spills), purposeful introduction (e.g., pesticide application, groundwater recharge, sewage sludge application to land, illegal discharge and dumping), and consumer activity (which includes both the excretion and purposeful disposal of a wide range of naturally occurring and anthropogenic chemicals, PPCPs being but one expansive galaxy of such chemicals). All of these sources but the last have long been recognized as major potential routes of pollutant release. Once released to the

environment, PPCPs (like other pollutants) can take up residence in "storage reservoirs," which can be viewed as secondary sources for further releases; examples are residues that have been concentrated by sorption to sediment, biosolids, or biota. Consumer activities, however, have only recently been recognized as a potentially major, long-standing source of uncontrolled nonpoint pollution.

An obvious source for PPCPs as environmental pollutants includes residues from their manufacturing. But since the discharge of pharmaceuticals and synthesis materials and by-products from manufacturing are already well defined and controlled in the U.S., they are not part of the scope of this chapter. The loss of the API during manufacturing is very small because APIs represent a significant monetary investment; in the U.S., the chemicals in manufacturing waste streams are primarily left-over intermediates and by-products from synthesis (none of which occurs in the final commercial product), not the drugs themselves. These emissions are all subject to existing regulations (see: EPA 1997, 2006a). For more information regarding manufacturing discharges, see EPA (1998).

It is worth noting, however, that of the major chemical synthesis industries, the pharmaceutical industry produces the most waste (from by-products, catalysts, solvents, salts, and intermediates) per unit of actual product. The ratio of waste mass produced per unit of API produced ranges roughly from 25 to 100. In comparison, for example, the petrochemical sector operates at a waste-per-product ratio of about 0.01. For proper perspective, however, the annual production volumes of final product (i.e., the API itself) are many orders of magnitude lower in the pharmaceutical sector, somewhere between 1 and a 1,000 tons (Poliakoff et al. 2002, using the E-factor approach adapted from Sheldon). The industry is also making continual progress in adopting green chemistry approaches in developing alternative synthesis routes for new and existing APIs.

When discussing quantities of drugs manufactured or disposed, it is important to recognize that the actual API represents only a portion of the overall mass of the finished formulated drug (which includes the other ingredients composing the finished drug, namely the excipients; see IPEC 2006). While manufacturing is indeed a potential source for APIs, albeit minor in the U.S., this chapter focuses on the importance of the activities, actions, and behaviors of the individual consumer and other end users of healthcare and veterinary medicines. The significance of the individual in directly contributing to the combined load of chemicals in the environment has been largely overlooked. PPCPs in the environment illustrate the immediate, intimate, and inseparable connection of the individual with the environment. These diffuse sources include the excretion of ingested drugs and bioactive metabolites, the washing of externally applied drugs and personal care products (e.g., see: Eriksson et al. 2003; EWG 2004), and the direct disposal of PPCPs to terrestrial sites and domestic sewage (Daughton 2003a,b). The importance of dispersed, diffuse, minute "discharges" of anthropogenic chemicals to the environment has been overshadowed for decades by the more obvious point sources.

Several factors are driving increases in usage of pharmaceuticals, at least in the U.S. These include: direct-to-consumer advertising (DTC); generic switches (reduced cost of medication previously available only by prescription); ease of access (Internet, black market); aging of the population (growing popularity of "anti-aging" pharmacy) and the consequent growing incidence of polypharmacy (e.g., as a necessity in geriatric medicine or as a result of patients retaining multiple providers, sometimes known as "doctor shopping" or "double doctoring"); new uses for existing drugs (e.g., lifestyle drugs and cosmetic pharmacology); increasing off-label prescribing (partly a result of the growing numbers of drug targets as revealed by genomics; one estimate gives at least 10 times as many potential molecular targets for future therapy than have been exploited to date, Drews 2000); distribution of medicines free of charge (e.g., to elderly patients as disease preventatives); and the continued growing use of illicit drugs and abuse of legal drugs. Trends for reducing usage include the advent of individualized (personalized) therapy (e.g.,

ability to test for polymorphisms, obviating the ineffective use of medication for certain sub-populations) and advanced technology for delivery of smaller doses directly to target sites.

Over the last decade, environmental scientists have established a large, diverse, and sometimes unexpected variety of pathways that serve to convey pharmaceuticals originating from the practice of human and veterinary medicine to various environmental compartments (e.g., see Figure 1). Despite the analogies and actual connections between human health and the integrity of our environment (Daughton 2003a), it is worth noting that little exists in the formal medical literature that explores the significance that the practice of medicine can have on the environment (Daughton 2002). Indeed, involvement of the medical community in the issues surrounding PPCPs should be considered a major objective for environmental scientists.

Tracing the sources of PPCP residues in the environment necessarily involves consideration of a broad spectrum of possible routes that connect their origination (at time of manufacture) to their deposition (or creation of transformation products) in the various environmental compartments, at which time they then acquire the potential to become involved with exposure of humans or the environment. These routes range from obvious ones, such as excretion of parent drugs and their metabolites, bathing, and purposeful disposal to sewerage, to more obscure ones, such as burial of heavily medicated bodies to the feeding of wildlife scavengers on discarded carcasses of euthanized or medicated domestic animals.

An examination of the sources of PPCPs in the environment poses a number of unresolved questions, many of which are highlighted in this chapter. These represent unmet needs defining future research. A compilation of research needs relevant to all the aspects of PPCPs as pollutants is available (Daughton 2004c).

SOURCES: General Considerations

Several dimensions define the scope of sources of PPCPs in the environment. As with most chemicals, PPCPs can find their way to the major compartments, including: (i) water (both ground waters and surface waters — lakes, rivers, streams, marine), (ii) solids (sediments and soils, including agricultural lands), (iii) air, and (iv) biota. With respect to air, the vast majority of drugs (in contrast to personal care products) have insufficient vapor pressures but they can gain entry to the air by dispersal while sorbed to fine particulates (e.g., medicated feed dusts used in confined animal feeding operations). Important to note is that both spatial and temporal dimensions exist for all sources. Some sources release transient, discontinuous spikes or pulses (especially disposal events), while others provide more continuous releases (e.g., excretion of a particular drug by significant portions of the local population), depending on the time scale of measurement, but nonetheless influenced by diurnal and seasonal patterns; an example of the occurrence of transient concentrations is shown by Lissemore et al. (2006). This consideration plays a critical role in the design of sampling protocols and can dictate whether small, discrete samples (e.g., grab samples) will be representative or whether time-and-space "integrative" sampling is required (Alvarez et al. 2004). These considerations determine whether the resulting data can be used to calculate accurate environmental fluxes or loads (e.g., "predicted environmental concentrations," PECs) required for environmental or risk assessments. Other dimensions include the levels, amounts, doses, or concentrations of PPCPs that different sources can contribute for an exposure event. Discussion of the risk assessment process (with a focus on veterinary drugs) is provided by Montforts (2005a,b).

The best-documented outcome from exposures is the possibility of chronic, low-level exposures (especially in the aquatic environment) that hold the potential primarily for subtle effects (Daughton and Ternes 1999). Others, however, can result in acute, high-level exposures, such as those resulting from the improper disposal or storage of PPCPs, or from the exposure of scavenging animals to drug-tainted

carcasses or medications improperly disposed in trash. Finally, some sources are best characterized as dispersed (e.g., release of residues via private residence sewerage) while others more resemble conventional point sources, such as private sewage leach fields, outfalls from sewage treatment plants, or confined (concentrated) animal feeding operations — CAFOs (see EPA 2004a for more information).

The distribution/supply chain for PPCPs, especially that for drugs, can be considered as well controlled and therefore an insignificant source for drugs in the environment. For drugs that remain unsold in pharmacies, the system of reverse distributors in the U.S. serves to ensure that unwanted pharmaceuticals are either returned to manufacturers or properly disposed according to regulations; for those countries without a reverse distribution system (Korea, for example see Rahn 2006), pharmacies must figure out how to dispose of expired pharmaceuticals themselves. For this reason, the fountainhead of sources for PPCPs as environmental pollutants in the U.S. begins with the consumer and other end-users.

The major route by which human-use PPCPs gain entry to the environment is from their intended, direct end-use. After systemic absorption due to topical, pulmonary, or parenteral administration or most commonly by ingestion, residues of the parent PPCP (as well as sometimes a complex array of metabolites) are either excreted or are dislodged from skin by sweating, bathing, or swimming (e.g., dermally applied drugs, such as topical antibiotics and hormones); even systemic drugs can be excreted through the skin, an example being the appearance of loratadine on the skin 40 minutes after ingesting a 10-mg oral dose of the antihistamine (Takáts 2004). With respect to excretion, these residues are associated primarily with the feces and urine (the relative partitioning between which depends on the pharmacokinetics of the individual drug), and less so via sweat, vomitus, and saliva. These residues include unmetabolized parent drug, bioactive metabolites (responsible for either intended therapeutic effects or adverse side effects), and inactive metabolites (including parent-drug metabolic conjugates, which can be subsequently hydrolyzed after excretion to release the parent drug; e.g., via microbial deglucuronidation via ß-glucuronidase; see: Auriol et al. 2006). Conjugates and parent PPCPs sorbed to sediments/particulates can essentially serve as secondary sources or hidden reservoirs.

The relative ratios among the different routes and of excreted forms can be dramatically altered by the health/disease status of the individual, as dictated by numerous factors including genetics, gender, age, and individual metabolic idiosyncracies, as well as by the formulation of the drug (e.g., some slow-dissolving tablet forms can lead to poor absorption and therefore enhance excretion of the unaltered parent drug). It is important to understand that the pharmacokinetics for a drug (as described by the absorption, distribution, metabolism, and elimination [ADME]) as documented in the literature can differ profoundly from reality as a result of the health status, diet, and genetics of the individual. Some of the many factors that dictate the absorption of a drug have been summarized by Surian (2006). Also of significance is that the extent of metabolism of a drug (and therefore the extent of excretion of the parent form) is not necessarily related to the frequency with which it is detected in the environment. Some extensively metabolized drugs (those for which only a very small percentage of the parent form is excreted, such as carbamazepine) can nonetheless establish widespread environmental occurrence (e.g., see: Bendz et al. 2005).

While consideration of sources tends to focus on parent, unaltered PPCPs, it is important to not disregard that many of the sources of parent PPCPs also serve as sources of transformation products — not just excreted metabolites, but also environmental transformation products such as from microbial metabolism and phototransformation ("degradates"). Consider carbamazepine (CBZ) as one example. Pharmacologically, CBZ is an extremely "dirty" or "promiscuous" drug, capable of eliciting numerous side effects as a result of its action on multiple receptors, partly as a result of a plethora of metabolites. Although carbamazepine-10,11-epoxide is the major initial (and bioactive) metabolite of carbamazepine, it is rather efficiently converted to the diol and a host of thirty-some other metabolites (Breton et al.

2005), some of which undoubtedly are responsible for the multitude of human side effects. While CBZ is extensively metabolized by humans (roughly only 3% of the parent drug is excreted unchanged), its introduction to the environment would likely be accompanied by numerous metabolites. Indeed, Miao and Metcalfe (2003) revealed the occurrence of five CBZ metabolites in the influent to sewage treatment plants: 10,11-dihydro-10,11-epoxycarbamazepine; 10,11-dihydro-10,11-dihydroxycarbamazepine; 2-hydroxycarbamazepine; 3-hydroxycarbamazepine; and 10,11-dihydro-10-hydroxycarbamazepine. The 10,11-dihydro-10,11-dihydroxycarbamazepine was also detected in surface water, at a three-fold higher level than the ubiquitous CBZ.

A secondary route by which PPCPs gain entry to the environment is by direct disposal. The primary routes for disposal are via flushing to sewerage from toilets (and other drains) and from discard to domestic trash, which is then usually buried in landfills. Note that while the majority of excreted urine and fecal material passes into sewage collection systems, a smaller but potentially significant portion is disposed to landfills by way of baby diapers and adult incontinence products; this constitutes another route of disposal to landfills (albeit of excreted drugs in contrast to unused drugs). Even properly engineered landfills can serve as delayed sources of drug residues, especially if leachates seep into the ground or are actively pumped out for disposal at water treatment facilities. Landfills and PPCPs have been discussed by Bound and Vouvoulis (2005). Disposal to sewerage occurs not just in domestic residences but also in certain healthcare facilities such as those used for long-term care. The driving forces behind the necessity of disposal include the expiration of medication, cessation of therapeutic need, and patients' "non-adherence" (non-compliance) such as discontinuation of medication because of adverse effects, failure to treat, or lack of motivation to continue therapy.

Little appreciated in the many aspects of work regarding PPCPs over the last decade or so is the critical importance of recognizing that the alternative to drug disposal from private residences is on-site long-term storage (e.g., in medicine cabinets and kitchens). Because of storage, PPCPs are responsible for a preponderance of poisonings in the U.S. for both children and adults. Detailed therapeutic-class and substance-specific data are maintained by the American Association of Poison Control Centers (AAPCC 2005). Since storage of PPCPs within domestic residences is a major contributor to accidental and purposeful poisonings for humans (adults, children, infants) and pets (e.g., see: ASPCA 2005), it is critical to minimize the quantities that are stored, and confine storage to proper areas; for example, conventional vials and bottles will not ensure pet safety, as dogs for example, can chew through plastic containers. Accumulation of multiple containers of drugs can become confusing, especially for older patients and minors, and increases the risk that the wrong medication could be consumed, especially for those practicing polypharmacy (see example presented later below).

Storage of PPCPs in healthcare facilities can also result in diversion to the black market. Storage of drugs in excess of those needed for immediate use also encourages abuse, a current example of which among teens is illustrated by the popularity of "pharming" (ONDCP 2005). Also worth noting is that prescription drugs are not necessarily the most hazardous PPCPs for infants and toddlers; for example, high-potency iron supplements and widely used OTC products (e.g., those containing acetaminophen and stimulants) are major causes of poisoning.

One of the most important aspects of the controversies surrounding drug disposal in the U.S. is the lack of recognition for the direct connection between ways to minimize the introduction of drugs to the environment and the ways in which properly designed storage and disposal programs could protect human health and reduce poisonings — environmental concerns aside. Strategies to facilitate the collection, inventory, and destruction of unnecessarily prescribed/purchased pharmaceuticals is a very important risk management tool, especially given its potential to mine information critical to continually reduce future medication errors, reduce accidental and purposeful poisonings, reduce abuse, reduce

controlled substance diversion, and reduce inappropriate and dangerous drug therapy resulting from the lack of appropriate diagnosis or prescribing by care givers.

In considering disposal as a source of environmental residues, while the major aspect probably involves discard of the unused medication (regardless of formulation), consideration must also be given to the concentrated residues contained in used dispensers and delivery devices (e.g., dermal patches, gel packs, bottles, pumps, inhalers, syringes); this is particularly relevant to hormonal preparations (e.g., testosterone, estrogens, progestins, and illegal anabolic steroids) and analgesic controlled substances (e.g., fentanyl). Toxicologically significant residues can remain in the used devices. Another minor consideration is the unintentional, incidental direct release of drugs and excipients simply as a result of correct usage of a product; examples are the release of propellants and volatile active ingredients to the air during use of inhalers and anaesthetic gases.

A tangentially related issue regarding sources, but one not covered here, is the fate of the packaging materials used for PPCPs, such as the materials used for plastic vials, IVs, and syringes, including the drug residues contained therein. Incineration and weathering of these materials are processes perhaps leading to a number of additional unknown products.

The Role of Source in the Perception of Risk

The significance of the real and perceived connections between our waste products with sources of drinking water and food can be greatly amplified by the presence of drug residues — regardless of how minute — as they can profoundly impact the perception of risk. In this respect, understanding the origins of these chemicals in the environment is extremely important and has ramifications with respect to our understanding of the water cycle (Daughton 2004a). Drinking water as a source of PPCPs, no matter how minuscule the concentrations, could be a key issue with regard to public acceptance (or rejection) of water recycled from wastewater (Daughton 2004a).

One of the ways in which risk is subconsciously framed or valued during its perception derives from a form of "logic" or valuation based on what are known as the "common laws of magic" (e.g., see: Rozin and Nemeroff , 1990). One of these laws is the Law of Association, which in turn comprises the sub-laws of Similarity and of Contact or Contagion. The "magical law of contagion" constitutes one of the sympathetic laws of magic as introduced over a century ago by anthropologists (see: Nemeroff and Rozin 1994). These “laws” partly originated with the alchemists. Of particular relevance to drinking water as a source of PPCPs is the Law of Contagion, which holds that once contaminated, always contaminated: "Things that have once been in contact with each other continue to act on each other at a distance even after physical contact has been severed." Once objects come into contact with each other, they will continue to influence each other, even after separation. The presence of PPCPs essentially serves as a reminder that the drinking water was at one time in "contact" with human waste. This can lead to rejection by the consumer of recycled water for drinking (Daughton 2004a; Kahn and Gerrard 2006).

SPECIFIC SOURCES:

The following provides a summary of the major sources for PPCP residues in the environment as well as some of those that are less discussed. The summary, however, should by no means be considered comprehensive. Previously unexpected sources are at times revealed. It is also important to note that the significance or magnitude of many of these sources is difficult to document, as they fall outside the normal domain of information addressed in the peer-reviewed literature; some are simply "common knowledge."

Beginning with the end user (or end use) as the ultimate source, the principal groups are consumers, healthcare providers, hospitals, veterinarians, and those working in agriculture (including farming, CAFOs, and aquaculture). Additional but less obvious sources exist, most of which have localized impacts. Examples are the accumulation of drugs donated during humanitarian relief efforts and the cemetery burial of bodies that have received large doses of drugs (including radionuclides).

Consumers: Already discussed above are the major routes from the consumer to the environment, primarily from excretion and direct disposal. With regard to the significance of disposal as a source, it cannot be overemphasized that current knowledge cannot establish the portion of PPCPs in the environment that originate from disposal versus excretion. This is a major unanswered question deserving some concerted investigation. Distinguishing flushed drugs from excreted drugs is currently not possible by chemical monitoring. Instead, this is currently achievable only by consumer surveys. But only rudimentary data from limited questionnaire surveys are available to offer some insights. These have been summarized by Daughton (2003b). These surveys have addressed the manner in which unwanted drugs are disposed by consumers but not the absolute or relative quantities that are actually disposed. The latter data are very scarce. For example, Berckmans et al. (1997) cite work claiming that about 40% of the drugs marketed in France annually remain unused, but with no reference as to what their disposition is.

The determination of the significance of disposal with regard to environmental loads is a major unmet research need — one that should be addressed if environmental residues are going to continue to be used as a justification for the need for comprehensive drug "take-back" programs in order to preclude disposal to sewerage or trash. It can probably be assumed that disposal might very well represent a significant source for a limited number of widely and heavily used, inexpensive drugs that can be purchased in large quantities (leading to expiration before they can be consumed); disposal probably does not represent a significant source for expensive drugs or for those that are unit packaged, but this is merely speculation.

Many factors lead to the storage of unwanted PPCPs in domestic residences. The level of adherence (compliance) by patients to prescribed medication regimes is one of the major factors that determines the accumulation and eventual expiration of unused drugs in the household, although the purchase of unnecessarily large quantities of OTC drugs is another reason (e.g., bulk containers). Adherence to medication is an extremely complex issue with a wide spectrum of causes. This important topic is discussed later.

Using non-compliance statistics as a starting point, the rate of disposal could eventually be indirectly inferred by determining the reasons for the non-compliance, as not all result in disposal. Only a portion of the reasons for non-compliance would lead to leftover medications that might eventually require disposal. For example, non-compliance results from the failure to take medications at the correct time or frequency, but neither of these failures on the part of the patient necessarily leads to leftover drugs. Another action classified as non-compliance is failure to have a prescription filled; this clearly would never result in leftover drugs.

Household surveys are another way to determine the portion of drugs that are disposed. There have been few such surveys conducted (see: Daughton 2003b). A recent survey of 400 households in England (Bound et al., 2005), found that nearly one half did not finish their course of medication. For those portions that were disposed and not stored indefinitely, nearly two-thirds were disposed to trash, about a fifth were returned to the pharmacy, and about one-tenth were disposed to sewerage. Disposal to sewerage, however, did vary depending on the type medication; for example, some classes (e.g.,

hormones) were either disposed to trash or returned to the pharmacy, with none being discarded to sewerage.

Theoretically, one possible way to directly determine by chemical monitoring the contributions to environmental loads of a particular drug originating from disposal versus excretion would entail analyzing for skewness in the relative ratios of optical isomers (the "enantiomeric fraction") from chiral drugs that are racemates. Such an approach would follow from the example of Sedlak and Fono (2004) and Fono and Sedlak (2005), who used enantiomer ratios from racemic metoprolol to distinguish sewage originating from waste treatment (the equi-enantiomer ratio is changed by selective action of biodegradation) from that of sewage having experienced no treatment (e.g., overflow events or straight-piping). Using this approach, sewage-influent drug residues from racemic drugs originating from disposal might be distinguishable from those that were excreted by having insufficiently enriched ratios of optical isomers (because of a lack of metabolic transformation). Another approach would work only on selected drugs — those that are extensively metabolized (where little of the parent drug is excreted). The discovery of parent drug residues in sewage would then be a likely indicator of direct disposal.

Also worth noting is that the private individual is the major contributor of illicit drugs to the environment. Illicit drugs have received surprisingly little attention from environmental scientists, especially given their unknown effects on aquatic biota. To date, only two publications have focused on illicit drug residues in an environmental context (Daughton 2001; Zuccato et al. 2005) but additional investigations are underway (e.g., see: Turque 2006).

Once a drug is disposed or excreted (along with its metabolites), it passes dissolved or suspended in sewage to engineered sewage treatment facilities, to septic facilities, leach fields, or directly into receiving waters (e.g., via illegal privies or "straight-piping"); straight-piping serves to maximize the availability to the environment of any PPCPs that are present since no treatment is used to remove residues. Raw, untreated sewage can also enter the environment from sewage distribution and treatment systems as a result of storm events (overflows), system failures, and overcapacity; this is a common problem in those locales with aging infrastructures or rapidly expanding populations. Sewage distribution systems are all prone to underground leakage, especially from decaying sewage distribution infrastructure. Together with private septic systems and leach fields, these serve as potential sources for groundwater contamination. A particular approach that some municipalities are designing to deal with sewage overflows involves large-diameter subsurface deep-rock storage tunnels for accepting diverted flows until the treatment capacity for the wastewater treatment facility is restored. These tunnels, like any subsurface sewage conveyance infrastructure, provide an opportunity for seepage of untreated waste into aquifers. Another source for introduction of residues to groundwater is active recharge (groundwater reinjection) using treated sewage (reclaimed water). Some of the problems associated with groundwater contamination and the perception of risk are discussed by Daughton (2004a).

At sewage treatment facilities, the residues are subjected to various treatment regimes (depending on the size and sophistication of the treatment plant), resulting in "removals" that range from nearly complete to nearly zero. The removal efficiencies are a function of the individual PPCP as well as the treatment process(es). Removal of PPCPs is essentially a collateral or incidental function of a sewage treatment plant, as these facilities were never specifically designed to remove exotic, bioactive xenobiotics.

Two principal effluents result from sewage treatment — one consisting of the liquid effluent and the other sludge. While the liquid effluent is usually discharged to surface waters, it is sometimes used for irrigation; PPCPs are known to occur in the reclaimed water and to accumulate in and migrate through irrigated soils at concentrations in the nanogram-per-gram range (Kinney et al. 2006). The

sludges are usually disposed to land, sometimes after being upgraded to "biosolids," a process intended to effect logarithmic removal of microorganisms but which also coincidentally reduces PPCPs (but to unknown degrees); the need for sludge disposal can be avoided only by incineration. Sludge disposal to land (even in the form of soil amendments or fertilizer) can result in leaching of residues into the ground or lead to contaminated wet weather runoff to receiving waters. Both the irrigation waters and the sludges derived from sewage can lead to direct exposure of organisms (e.g., worms and insects). Plants can also systemically absorb PPCP residues (Boxall et al. 2006; Jjemba 2002). A third waste stream that can result from water treatment (primarily for drinking water) is the brine rejection stream from membrane filtration; the concentrations of PPCPs as well as large numbers of other pollutants will be enriched in these streams and therefore require special attention.

The many questions associated with the disposal of drugs often raise some of the very same questions for personal care products. Personal care products (PCPs) are analogous to pharmaceuticals in that their intended end-use can distribute to the environment the ingredients that compose their formulations (e.g., see: EWG 2004), as well as the chemicals contained by their packaging. But unlike most drugs, this occurs primarily not by excretion, but rather by washing the product from skin, hair, and mouth, where its ingredients (both active and inactive ingredients) can then enter the environment via the sewerage pathway. Packaging used for personal care products, which is usually much more elaborate and substantial than for drugs, is discarded to trash where it can eventually weather, with the resulting release of additional chemicals from the combined actions of microbial degradation (especially fungal), UV photolysis, physical deterioration (e.g., action of heat), and chemical processes (e.g., leaching by water). PCPs also contrast with pharmaceuticals in that the latter are produced in relatively small quantities (sometimes as low as the kg/year range) and are largely designed to be biologically active. PCPs, in contrast, are more similar to high-volume chemicals, are not purposefully designed with bioactivity, and comparatively less is known regarding their interactions with organisms (in part because this is not always registration requirement).

With regard to environmental ramifications, PCPs (such as cosmetics) can differ from pharmaceuticals in three major respects: (1) the design of the packaging discourages disposal of the contents to sewage (because of the added difficulty of emptying package contents), (2) the "active" ingredients in PCPs are generally not engineered or designed to interact with biological receptors that regulate essential cellular functions, and (3) PCPs are used predominately external to the body. When applied to skin or the mouth, however, those chemicals in PCPs that are lipophilic are subject to absorption through the skin or mucosal membranes (e.g., parabens, phthalates, UV screens, and synthetic musks). Indeed, one of the paradoxes of consumer risk perception relates to the relatively high concentrations and plethora of types of chemicals formulated in personal care products that are applied directly to the skin, versus the concentrations of some of these same chemicals that might be found in drinking water, but at many orders of magnitude lower concentrations; the former is often deemed risk-free by the consumer but the latter not.

Unlike pharmaceuticals, mainly as a result of the packaging design and the way in which they are used, the disposal of unused or unwanted PCPs (e.g., cosmetics, shampoos) to sewerage has not been a concern with regard to the potential for environmental pollution. With this said, the ingredients comprising PCPs (both the active ingredients and the so-called "inactive" ingredients) are used in much larger quantities in end-user commercial products than are pharmaceuticals. These active ingredients and even some of the inactive ingredients pose the potential for exposure to aquatic organisms (from residues discharged with sewage) and to terrestrial animals (by scavengers foraging in municipal refuse). The UV-filters used in sunscreens serve as one example (Balmer et al. 2005; Buser et al. 2006). Substantial, sustained exposures pose unknown risks (e.g., subtle effects such as behavioral change) for certain organisms, especially those that are subject to continual exposure, such as aquatic organisms; this is

especially true for lipophilic compounds that can bioconcentrate. An important perspective to maintain, however, relates to those ingredients that share the same mechanism or mode of action. For example, the alkylphenolethoxylates used extensively in PCPs have extremely weak estrogenic activity compared with the estrogenic drugs, but their environmental residue levels are also far greater. To determine relative exposure risks, both potency and concentration need to be considered in tandem.

With regard to the disposition of PCPs in the environment, the principles that could guide the creation of products that are most environmentally friendly would be those that fall under the stewardship concept of "cradle-to-cradle design" (Daughton 2003a,b). This ecologically intelligent design paradigm, as formulated by McDonough and Braungart (2002), can be applied not just to the ingredients used in formulating these products, but also to the design and composition of the packaging and to the way the final product is distributed and consumed in the distribution commerce chain. For example, the types and amounts of materials used in manufacturing the packaging itself could be selected for minimal environmental impact (whether that be the sheer volume of packaging added to landfills, or the chemicals released by weathering, or by combustion of refuse packaging). At the same time, the packaging can be designed to maximize the consumer's ability to use the contents to the fullest extent possible, ensuring that the ingredients are directed to sewage treatment facilities (e.g., during bathing) where they can at least be degraded, rather than discarding partially empty containers in the trash.

Consumer PCPs also illustrate the potential importance of the so-called "inactive" or "inert" ingredients (such as the solvents/carriers) with regard to unanticipated exposure routes. PCPs are becoming established as a source of previously unrecognized air pollution. Although the active ingredients in PPCPs (with the exception of certain anaesthetic gases and synthetic musk fragrances) are probably without impact on air, the more prevalent "inert" ingredients can contribute to general indoor air pollution and serve as precursors to smog. California regulators, for example, are becoming more cognizant of the individually minuscule but significant combined effects of the chemicals released by consumerism (CARB 2005).

Finally, with regard to consumer use, PCPs can also serve as significant sources for conventional pollutants. Obvious examples include: phthalates (especially diethyl and dibutyl), solvents, dyes, and parabens (4-hydroxybenzoic acid alkyl esters), all of which are commonly used in dermal products; alkylphenolic surfactants (major ingredients in shampoos and soaps); pesticides (some of which are used as PPCPs); lead (Pb) and other metals, which can comprise significant percentages by weight of various Ayurveda and folk remedies. Lead (Pb) in particular is used in litargirio (or litharge), sometimes at upwards of 80% by weight (Oregon DHS 2005; Saper et al. 2004); likewise, mercury is used in certain (banned) skin-lightening creams and disinfectant soaps (upwards of 3% mercuric iodine, wt/wt, in soaps and 10% ammoniated mercury in skin lightening creams) (DOHMH 2005; Harada et al. 2001). Metals and organometallics are also used in pharmaceuticals, one of the more notable instances being ethylmercury (as ethylmercurithiosalicylate-sodium, Thimerosal), added as a preservative to certain vaccines; others include barium and lithium. Extractables and leachables in dispensing devices and containers can also be a significant source of certain conventional chemicals (e.g., plasticizers, nitrosamines, and acrylonitrile, deriving from plastics adhesives, antioxidants, coatings, vulcanizers, accelerants, adhesives). Worth noting is the significant distinction between EU and U.S. policy in the regulation of cosmetics, as reflected by the hundreds of ingredients in U.S. cosmetics that are not permitted in EU products as a result of potential linkages with genetic or reproductive effects.

Healthcare Providers: The major sector of the healthcare community that contributes to the environmental load of PPCPs is probably long-term care facilities (LTCFs) and hospices, a topic discussed by Daughton (2003b). Patients at LTCFs are often under the care of multiple physicians and receive multiple medications (polypharmacy). Their prescriptions are also subject to frequent change,

resulting in unusually large amounts of unused medications. LTCFs often dispose of unused medication to sewerage (in some states this is a legislated requirement), especially if the drug is a controlled substance. Physicians (and dentists) also sometimes dispose of out-dated manufacturers' samples and pharmaceuticals used in-practice to sewerage and to trash; pharmacies are minor sources, as they can use the reverse-distribution system and must also abide by laws (e.g., RCRA; Smith 2006) regulating the disposal of hazardous waste (see: Daughton 2003b). Improved efficiency in the way drugs are dispensed at LTCFs, namely with computerized unit-dose dispensing, could greatly reduce the quantities needing disposal. LTCFs are an example of a point-source that could have ramifications at the local level.

Hospitals: The medications used in hospitals differ with respect to their types, doses, per-capita consumption, and relative quantities consumed compared with those used by the consumer. These drugs are weighted toward those with higher acute toxicity and genotoxicity (e.g., cytotoxics, oncolytics) and which are used for short-term therapy and diagnostics (e.g., radionuclides), rather than toward long-term maintenance. For this reason, the suite of drugs that occur in waste streams from hospitals can differ in both classes and quantities from those emanating from private residences. Locales having a confluence of hospitals may pose unique circumstances for municipal waste treatment plants and their effluents, depending on whether the hospitals practice waste pretreatment and how sophisticated the pretreatment might be.

Veterinarians: The complete list of drugs available for use with animals in the U.S. is captured in the *Green Book*, which is published by the FDA's Center for Veterinary Medicine (FDA 2005d). Key information regarding the environmental assessment of veterinary pharmaceuticals [i.e., formal Environmental Assessments (EAs), Findings of No Significant Impact (FONSIs), and Environmental Impact Statements (EISs)] can be found at FDA (2006). While there is significant overlap among the drugs used in veterinary and human medicine, some are unique. Veterinary use of drugs leads also to some unique sources and routes of exposure. Veterinary use of drugs for domestic animals, such as pets, leads to the direct deposition of residues on land via excrement; any drug residues are then subject to entrainment in wet-weather run-off to storm drains or receiving waters.

While the primary significance of veterinary drugs in the environment derives from their routine usage with raising domestic animals for commerce (and the resulting issues concerning CAFOs, grazing livestock, and aquaculture), the consequences for some veterinary uses have involved significant but little recognized instances of acute poisonings of wildlife. Two examples illustrate the profound ecological consequences that can result from these sources. One is the improper discarding of carcasses from animals that have been euthanized or heavily medicated. The principle drug used for animal euthanasia is pentobarbital. High doses are used, and most of the body-burden residue escapes excretion and persists indefinitely in the body. If not disposed properly, the carcasses can be consumed by scavenger wildlife. But determined wildlife can even uncover well-buried carcasses. Wildlife pentobarbital poisonings had been recorded in at least 14 states since the mid-1980s, the U.S. Fish and Wildlife Service at one point having documented more than 130 bald and golden eagle casualties. Wildlife vulnerable to accidental pentobarbital poisoning (or to any other drug used for euthanasia) include a wide range of birds (especially eagles), foxes, bears, martens, fishers, coyotes, lynx, bobcats, cougars, and otters. Domestic dogs can be poisoned, and zoos have documented the deaths of tigers, cougars and lions that were accidentally fed tainted meat. As a result, in July 2003, the FDA's Center for Veterinary Medicine required an environmental warning to be added to animal euthanasia products (FDA 2003).

A second example is the massive poisonings of vultures in Southeast Asia by their feeding on carcasses of cattle that had been treated with diclofenac. Beginning in the early 1990s, vultures (especially white-backed vultures such as *Gyps bengalensis*) experienced dramatic population declines (as great as 95%) in Southern Asia. The causative agent had led to acute renal failure (manifested as

visceral gout from accumulation of uric acid), leading to death of the breeding population. At least some of these die-offs were eventually linked to poisoning with diclofenac (Oaks et al. 2004). Although primarily a human anti-inflammatory in the U.S., diclofenac was used in veterinary medicine in other countries. In India, diclofenac was used for cattle, whose carcasses are a major food source for *Gyps*. Diclofenac seemed to be selectively toxic to *Gyps* spp. versus other carrion-eating raptors. As of 2005, India committed to phasing out the veterinary use of diclofenac.

These two examples show some of the unexpected routes by which PPCPs can gain access to the environment. They also show the types of unanticipated, acute ecological effects that can occur from seemingly innocuous drugs and their routine usage.

Agriculture and Aquaculture: Drugs are widely and heavily used in a spectrum of agriculture practices. But unlike with human use, the numbers of targeted biological endpoints are limited. Although there are human drugs from a wide spectrum of therapeutic classes, agricultural use tends to focus on antibiotics and steroidal hormones. Discussions in the literature of environmental aspects of drugs used in agriculture are usually separate from those used in human medicine. It is important to recognize, however, that many of the drugs used in agriculture and human medicine are identical or belong to the same chemical classes; some, however, have exclusive uses. The residues that get introduced to the environment also hold the potential for effecting ecological and human exposures. What sets agricultural uses apart from others are the quantities of drugs that can be released and the localized manner in which they are released (e,g., with CAFOs) and during open-range grazing (e.g., impacting run-off to local water bodies). Especially unique for agricultural use is that drugs can be introduced directly to the environment as a direct result of their use, similar to pesticides (e.g., crop spraying and aquaculture). Aquaculture can release drugs directly to open waters (from excess medicated feed and from excreta). In contrast to human use, agricultural introduction via CAFOs tends to be localized, more resembling point sources. Aquaculture also experiences off-label and illegal usage of certain drugs (e.g., see FAO 2002), especially highly toxic antibiotics such as chloramphenicol, furazolidone, and nitrofurazone, all of whose use is banned in many countries but continues nonetheless; this source can lead to direct human exposure via consumption of contaminated fin and shell fish). For thorough background on the environmental aspects of concentrated aquatic animal production (CAAP) and the role of pharmaceuticals, refer to the materials available from EPA (2006b), and in particular EPA (2004b). In contrast to human use, agricultural use also poses concerns with regard to occupational exposure, an example being the inhalation of medication sorbed to dust particles generated by the handling of medicated feeds (Hamscher et al. 2003).

Agricultural use of drugs ranges from crops (e.g., use of antibiotics for plant disease control), CAFOs (antibiotics and estrogenic and androgenic steroids, for both therapeutic treatment and growth promotion), and aquaculture (e.g., antibiotics for disease prevention and treatment). A major unknown is the relative portions of residues (especially antibiotics) in the environment that emanate from agricultural versus human use. As with determining overall drug usage rates (in terms of quantities), unequivocal statistics are not even available for the usage rates (e.g., for antibiotics) by agriculture versus others. A major issue with regard to CAFOs is the integrity of lagoons and other storage areas that detain or treat wastes from CAFOs. These wastes can contain high levels of PPCPs as well as endogenous hormones (especially estrogens and their conjugates). The holding areas (lagoons) are vulnerable to overflow during extreme wet-weather events as well as leaching to groundwater. Manure and sludges are also widely dispersed as amendments or fertilizer to land. An approach for prioritizing the veterinary medications deserving concerted attention with respect to assessing human exposure has been presented by Capelton et al. (2006).

Potential sources for human exposure include not just drinking water and the well-known but less publicized routes such as domestic livestock and fish treated with veterinary drugs, but also the less-known route of edible plants. When excrement from domestic animals treated with veterinary medicines is used on arable lands (e.g., as soil amendment or fertilizer), plants have the potential to remove the drug residues that partition to the soil pore water. These residues can accumulate in shoots and roots. For a limited number of targeted drugs evaluated under controlled conditions, the residues found to accumulate in certain plants were calculated to hold the potential for yielding intakes that approached 10% of the accepted daily intake (Boxall et al. 2006).

A related issue regarding agriculture as a source involves "plant-made pharmaceuticals" (PMPs) derived from the crop-based transgenic production of proteinaceous therapeutics by genetically altered plants ("molecular farming" — "biopharming"). Current transgenic biotechnology has the potential for using food crop species (primarily corn, soybeans, rice) for producing hundreds of distinct proteinaceous therapeutics (especially enzymes, hormones, vaccines, monoclonal antibodies). PMPs raise a host of questions regarding risk, primarily centered around allergenicity and consumer toxicity in the form of direct endocrine disruption or other mechanisms. Less-recognized concerns include possible hazards to non-target organisms (e.g., foragers and insects), whose interactions with crops are extremely difficult to prevent. Drugs based on peptides and proteins would ordinarily not be expected to persist in the environment because they are easily degraded. A possible exception is the cyclic peptides and circular proteins. Natural products of the former include cyclosporin (an immunosuppressant) and gramicidin S (an antibiotic); these are distinguished from the circular proteins in being synthesized by enzymatic pathways as opposed to being synthesized ribosomally. Synthetic versions of these chemicals (which cross over into the domain of self-assembling nanostructures) can be designed with broad-ranging biological activities, especially antimicrobial. The significant aspects of this class of drugs is that they resist chemical, thermal, and enzymatic alternation and therefore have the potential to persist in the environment.

Miscellaneous Sources: There are probably numerous miscellaneous sources for drugs in the environment, such as from the discharge of sewage (both treated and raw) from cruise ships. Such sources are characterized by being insignificant with respect to contributing to overall environmental loads but in certain localized situations could prove significant with respect to the ecology. Two examples serve to illustrate the range of ways in which miscellaneous sources can be unforeseen. First is the accumulation of drugs donated during humanitarian relief efforts. Drug donations have long proved problematic to humanitarian efforts because of the sometimes massive quantities of inappropriate or outdated medications, or simply because of large surpluses that cannot be used before expiration. Thousands of tons of drugs are sometimes received and necessitate storage and eventual disposal; this is discussed further in the second section of this chapter. A second example, but one that could only have a possible effect on local groundwater, relates to the burial of bodies in cemeteries. Bodies can sometimes serve as reservoirs of large quantities of multiple drugs if heroic life-saving measures had been attempted. More detail on these examples (and others) is provided in Daughton (2003a,b).

Another example pertains to "manufacturing." An exception to manufacturing being an insignificant environmental source of drugs is the release of certain highly potent drugs and chemical synthesis agents from illegal, clandestine drug laboratories ("clan labs"). The growing problem of clan labs, especially for methamphetamine, continues to reveal a wealth of previously unrecognized sources, including those labs that are mobile or easily hidden. While clan labs can release hazardous amounts of synthesis ingredients to the environment, the amount of the active ingredient itself that is accidently or purposefully discarded is unknown. Buildings that are used for meth labs, however, can pose acute risks to first responders, clean-up crews, and even to those who subsequently occupy the structures after remediation has been attempted, because of the large quantities of methamphetamine that have been

absorbed by porous building materials (e.g., concrete and masonry) and which slowly migrate back to the surfaces.

Related to clandestine drugs is the escalating occurrence of counterfeit drugs, a problem also partly related to drug importation and drug diversion. Although counterfeit drugs often comprise non-pharmacologic ingredients (but sometimes harmful), they sometimes contain active ingredients (sometimes sub-potent, sometimes a different drug) (Hileman 2003). The analogous problem exists with nutraceuticals and food supplements, which are sometimes adulterated with drugs; one example was the marketing in 2003 of an OTC dietary supplement (Viga) that actually contained sildenafil.

Finally, new technologies introduced to medicine hold the potential to serve as previously unanticipated sources of new types of chemicals. A totally new class of chemicals being introduced to medicine are those comprising nanoscale materials (nanomaterials). These materials are touted as presenting unprecedented, revolutionary opportunities for medicine. In contrast to "conventional" chemicals, the properties of these materials are dictated more by their molecular or particle size and shape than by their chemical structures or compositions. Nanomaterials comprise particles with diameters ranging roughly from 1 nm (10 Angstroms, about the size of 10 hydrogen atoms) to 100 nm. The advent of "nanomedicine" holds the potential as another source of medically related materials in the environment. Current applications include vastly improved delivery of drugs to target organs and tissues, thereby improving therapeutic outcomes and minimizing side effects and adverse reactions — all with greatly lower doses. Futuristic uses are vast, including the use of "nanobots" that can roam and diagnose disease, monitor health status, correct cellular defects, repair damaged tissue, or enhance biological performance, or that can be used in the fabrication of biocompatible materials that substitute for biological tissues. While nanotechnology holds the potential to reduce the introduction of conventional drugs to the environment, the environmental ramifications of these materials themselves include release of totally new types of pollutants derived from the manufacture, use, and weathering of nanomedicines and nanodevices (Daughton 2004b).

Multiple Aggregate Sources: Some drugs can have multiple origins, which pose opportunities for aggregate exposure. A special case includes those chemicals that have dual uses as therapeutants and as pesticides. Examples include: triclosan/triclocarban (broad-spectrum antimicrobials used as general biocides; triclosan is also used as a gingivitis agent used in toothpaste); 4-aminopyridine (an experimental multiple sclerosis drug and avicide); warfarin (an anticoagulant and rat poison); azasteroids (antilipidemics and avian/rodent/insect reproductive inhibitors); certain antibiotics (control of orchard pathogens); acetaminophen (analgesic and control of the Brown Tree snake: Savarie et al. 2001); caffeine (stimulant and used experimentally for control of the *Coqui* frog in Hawaii: USDA 2003; also repels and kills snails and slugs at concentrations exceeding 0.5%: Hollingsworth 2002); lindane and permethrins/pyrethrins (insecticide and control of ticks, fleas, and body and head lice as a shampoo ingredient); and nicotine (a broad spectrum insecticide).

DATA NEEDS

Comprehensive data on PPCP sources is key to understanding and predicting the occurrence of PPCPs in the environment (which can be done via modeling and by directed target-based monitoring). It is also important for understanding the best approaches for reducing accidental poisonings from stored medications or from those being improperly disposed. In this regard, nation-wide databases, based on geographic information systems, would be invaluable. An ideal system would provide real-time prescription and OTC sales/usage and disposal data. In the U.S., neither the absolute usage rates for PPCPs nor their geographic variations are available in public databases. Geographic drug usage patterns are partly a function of local prescribing customs, patient preferences and fads, and distribution of disease and illness. A real-time GIS database showing drug usage by geographic locale would greatly aid

modeling and monitoring efforts; but the proprietary nature of the pharmaceutical industry, widespread OTC availability of veterinary and agricultural drugs (especially antibiotics), and the availability of drugs from outside manufacturer distribution networks (e.g., via the Internet, foreign countries, and black markets) are major barriers to gaining accurate information. Understanding geographic anomalies in prescribing and usage is important as it could result in localized residue levels that are higher than the PECs predicted on the basis of geographically unbiased usages (Daughton 2003a).

1.1.2 Means for minimizing these sources (e.g., pollution prevention)

With better understanding of the sources or origins of PPCPs as pollutants, those sources most amenable to lessening or minimizing their connections with the environment can be identified. Pollution reduction (or minimization) encompasses a wide range of actions, including reduced dosage, waste treatment, waste containment/storage (which often is simply a form of pollution "postponement"), recycling/re-use, disposal, and pollution prevention (also known as source reduction). Note that the formal definition of pollution prevention itself does not include any of the aforementioned activities, but it is distinguished by serving to eliminate or reduce the need for those activities.

A wide spectrum of actions and activities could be designed and implemented to reduce the environmental residues contributed from many of the major sources of PPCPs. These pollution reduction approaches fall into all of the primary categories just listed. Among these categories, a wide spectrum of approaches for pollution prevention, aimed at all aspects of the regulated distribution/sales chain (which spans drug discovery, manufacturing, packaging, distribution, dispensing, and retailing) as well as how a drug is formulated and administered have been summarized by Daughton (2003a,b,c). As for the other categories (especially waste treatment), they have been covered in many other publications, including this book and several prior books (e.g., Daughton and Jones-Lepp 2001; Kümmerer 2004). As but one of numerous possible examples, alternative delivery mechanisms, such as intranasal (which bypasses first-pass hepatic metabolism) can be used for better targeting the dose and thereby reducing dosages and minimizing undesirable metabolic products.

The remainder of this chapter will therefore focus on the two categories that have generated the most attention in the U.S. — disposal and re-use — both of which come into play once a drug exits the regulated sales chain and enters the largely unregulated realms of the consumer and other end-users. Although these two topics have also been covered in Daughton (2003a,b), various aspects will be developed in more detail here.

DRUG DISPOSAL

The disposal of drugs by consumers has been a controversial and confusing topic in the U.S. for two major reasons. First, a number of federal and state regulations limit the options available for disposal of unwanted drugs. Analogous regulations do not exist in many other countries. Second, because of these imposed constraints, selecting "prudent" options for drug disposal forces a mutually exclusive choice between ensuring public safety and protecting ecologic integrity. No widely available, cost-effective mechanism or procedure is currently available to do both. In distinct contrast, note that drug disposal in certain other countries is handled in a straightforward manner with "take-back" or "returns" programs, where consumers simply return their unwanted PPCPs to drop-off points such as local pharmacies. Consequently, much of the following discussion pertains primarily to the U.S.

The need for a simple, universal option for disposing of unused medications is driven by the following considerations and scenarios, all of which are all known to occur as a result of either storing leftover medications or of improper disposal: (i) accidental (and sometimes purposeful) poisoning of infants,

children, adults, pets, and wildlife, (ii) increased risk of medications being used past expiry (at which time their efficacy can decrease and/or toxicity can increase), (iii) accumulation of multiple drugs (even if they have not expired) increases the chances of adverse drug interactions, especially if polypharmacy and self-medication are practiced past the date when the original prescription was intended, (iv) accumulation of multiple drugs (even if they have not expired) increases the chances of improper self-medication simply as a result of confusion (this is a long-standing problem for the aging population, especially for those practicing polypharmacy) (v) stored drugs encourage self-medication by those for whom they were not prescribed, increasing the risk of adverse events, (vi) accumulation of stored drugs increases the risk of burglary (by those seeking drugs) and of diversion (e.g., "pharming" parties), and (vii) leftover drugs are a symptom of inefficiencies and/or errors in physician prescribing or patient compliance, and as such, represent increased costs for the healthcare community and consumers as well as reduced or jeopardized therapeutic outcomes.

Prior to any discussion of drug disposal, it is critical to understand the motivation and perceived need driving "environmentally sound" practices for drug disposal. Key to this is recognizing that the portion of environmental drug residues originating from direct disposal by consumers and other end users compared with the portion originating from excretion and bathing is simply not known. The relative contributions to environmental loadings from direct (controllable) disposal of unwanted PPCPs (to sewage and trash) versus indirect (involuntary or inadvertent) excretion and washing to sewerage are known neither for the total environmental burden of PPCPs nor for specific, individual drugs. Does this fraction vary from drug to drug, or among packaging types (e.g., bulk bottles versus blister packs)? The relative significance of direct disposal versus excretion is therefore a major question whose answer is important with regard to justifying drug disposal or take-back programs. This consideration has been overlooked by all assessments made to date of drug disposal, and it represents one of the numerous research needs for the many facets of PPCPs as environmental pollutants (Daughton 2004c) and as highlighted by Daughton (2003b). In the absence of this data, the inability to predict the outcome (if any) that might result from successfully implementing a nationwide, environmentally sound disposal program is problematic. This would be the case even if the disposal of drugs to sewerage or trash were completely eliminated.

It is possible that direct disposal may indeed be a significant source of environmental residues for a limited number of drugs, such as for OTC medicines (especially those that are bulk purchased in such large quantities that they expire before being completely used) and for those drugs that are extensively metabolized, resulting in little of the parent drug being excreted. In contrast, disposal is probably not a significant source for those drugs provided by unit dispensing, for those that are costly or prescribed in short courses, or for those that are largely excreted unchanged. **It is quite possible, therefore, that even if environmentally sound drug disposal could be implemented, the resulting reduction in overall environmental loads of PPCPs might be negligible (at least for most drugs)**. This prompts the obvious question of why options such as take-back programs are needed or desired, especially if they are perceived as adding further cost to health care. The answer is several-fold.

The desire to minimize ecological exposure to PPCPs is not the only driving force behind the need for prudent drug disposal. Two others drivers are: (1) the need to protect human safety (e.g., accidental and purposeful poisonings made possible by unwanted drugs that are stored and not disposed), and (2) the public's fundamental desire to be proactive in removing as many possible xenobiotics from the environment (especially from drinking water sources), regardless of any known adverse toxicology. This latter point is important and reveals a fundamental relationship of society with chemicals in general — namely that aversion to involuntary or inadvertent chemical exposure to certain chemicals, even in the stark absence of any known hazard, can result **solely because the chemicals occur where they are not expected or desired**. Such substances have been termed "chemical weeds" (Daughton 2005).

It is also important to keep in mind that prudent drug disposal is but one of many possible facets of a larger, holistic environmental stewardship program (Daughton 2003a,b,c). A multiple of pollution prevention approaches can be applied to the many facets of the existing production-distribution-consumption chain for PPCPs. These facets include everything from drug design, drug manufacturing (e.g., green chemistry approaches), drug delivery, package design, distribution, prescribing (e.g., individualization of therapy), dispensing, marketing/advertising, patient compliance, education for health care practitioners, disposal, to data mining (e.g., from unused medications) and others. Implementation of one or more of these stewardship measures (in addition to proper drug disposal) affords two more possible advantages:

(a) Improvement in therapeutic outcomes and patient health, as well as reducing healthcare costs; these are part of the philosophy behind cradle-to-cradle stewardship (Daughton 2003a). A holistic stewardship program also could yield collateral benefits for consumer/public health, such as by improving the awareness of the consumer and the medical community of environmental ramifications and increasing the prudent use of drugs.

(b) Possible achievement of even greater reductions in PPCP loadings to the environment than by drug disposal alone. In fact, it is worth asking if the resulting reduction in human and ecological exposure from such a stewardship program could be accomplished with far less investment of resources than required for further research (e.g., environmental toxicology) and development of end-of-pipe control technologies. A stewardship program designed for minimizing the introduction of PPCP residues to the environment might be particularly advantageous for dealing with the foreseeable increase and expansion in drug usage (e.g., as the population ages and as new therapies continue to be developed).

A suitably designed drug take-back program would be capable of improving overall health care and lowering health costs. This would be accomplished by inventorying returned drugs and the reasons for their return. Every medication that goes unused, eventually needing disposal, represents a prescription or purchase that was either not needed or not complied with. Either represents wasted health care resources and the possibility of adverse or suboptimal therapeutic outcomes. By mining the information that could be obtained from drug returns, knowledge could be developed for continually adjusting and improving prescribing practices and for lessening health care expenditures. The data that can be obtained from drug returns can also be used in prioritization models for selecting those drugs being used (or disposed of) most frequently in particular geographic locales and which might therefore have a significant environmental presence. This can then better guide and tailor the selection of drug targeted for environmental monitoring. An example of the type of information that can be obtained just from a small, local take-back event is available from NERC (2005).

Currently, the only aspect of PPCPs known to directly impact human morbidity and mortality is their major contribution to accidental and purposeful poisonings (AAPCC 2005). One of the factors determining or encouraging inappropriate or undesired access to drugs is the prevalence of improper storage or misguided attempts at disposal, which is in turn caused by the accumulation of left-over drugs. Many factors lead to the unnecessary storage of unwanted PPCPs in domestic residences. The level of adherence (compliance) by patients to prescribed medication regimes is one of the major factors that determines the accumulation and eventual expiration of unused drugs in the household. Adherence to medication is an issue of great importance to healthcare. Its causes are many and complex (e.g., see: Kenreigh and Wagner 2005). A variety of ways to improve compliance, ranging from simple to technologically sophisticated, currently exist or are under development (e.g., see: Ukens 2005).

The critical importance of medication adherence is shown by the fact that one to two thirds of all hospital admissions in the U.S. related to medicine result from poor medication adherence, leading to medical costs of about $100 billion per year (Osterberg and Blaschke, 2005). An unknown portion of non-adherence, which undoubtedly varies wildly among classes of drugs (e.g., being roughly 50% for

long-term medications prescribed for chronic conditions), is one of the contributing factors to the accumulation of unused drugs in the household and therefore contributes to their direct disposal. The information that is completely lacking is the percentage of medications (once purchased) that are never used.

Once the consumer has accumulated a certain number of unuseable or unwanted medications in the home, the question of disposal is confronted. Conflicting needs and motivations make disposal of PPCPs a confusing issue. Water treatment facilities increasingly no longer want drugs unnecessarily discharged via sewers, while at the same time poison control centers have long-advised against discarding them to trash and have always recommended discarding to sewerage (since this is historically the easiest means available for protecting humans and pets from accidental and purposeful poisonings). Drugs discarded to municipal trash/landfills pose not just future environmental exposure risks but also ongoing risks with regard to re-use by those who scavenge for them (e.g., human "gleaners" or animal scavengers). Discard to sewerage, in contrast, is also the surest simple means for preventing drug diversion.

Solutions to the drug disposal quandary might seem to be easily addressable. However, an array of local, state, and federal regulations — promulgated to ensure occupational and consumer health, safety, and privacy — make any solution much more challenging. Statutes that must be considered include: (i) Federal and State hazardous wastes regulations, (ii) Controlled Substances Act (CSA, see below) as administered by the Drug Enforcement Administration (DEA); (iii) State regulations for long-term care facilities (where disposal to sewerage is sometimes required by law; see Daughton 2003a); and (iv) HIPAA, the Health Insurance Portability and Accountability Act; for HIPAA, it is unclear whether any recommendations that might be made to consumers regarding disposal must also inform them of the privacy protections afforded by HIPAA; for example, should patients be encouraged to remove their personal information, but not the prescription information, from drug labels prior to disposal.

The DEA regulates certain drugs under the Controlled Substances Act of 1970 (DEA 2005a), which classifies these drugs within five "Schedules" (I-V); note that Schedule I is reserved for those drugs having no recognized medical use and which are therefore deemed to be the most dangerous. The CSA through a series of amendments also regulates a list of chemicals that are used in the illicit synthesis of controlled substances. Several of these "listed chemicals" also happen to be non-controlled active ingredients of licit OTC drug products; these include ephedrine, pseudoephedrine, and phenylpropanolamine. Once prescribed, a controlled substance cannot be transferred to any other entity (including the original prescriber, a pharmacy, reverse distributor, or even a hazardous waste facility) other than DEA-"exempted" law enforcement. "The CSA also creates a closed system of distribution for those authorized to handle controlled substances. The cornerstone of this system is the registration of all those authorized by the DEA to handle controlled substances. All individuals and firms that are registered are required to maintain complete and accurate inventories and records of all transactions involving controlled substances, as well as security for the storage of controlled substances." (DEA 2005a)

"The overall goal of the Controlled Substances Act (CSA) and of DEA's regulations in Title 21, Code of Federal Regulations (CFR), Parts 1300-1316 is to provide a closed distribution system so that a controlled substance is at all times under the legal control of a person registered, or specifically exempted from registration, by the Drug Enforcement Administration until it reaches the ultimate user or is destroyed. DEA achieves this goal by registering manufacturers, distributors, importers, exporters, and dispensers of controlled substances as well as analytical laboratories and researchers. Thus, any movement of controlled substances between these registered persons is covered by DEA regulations, which ensure that all controlled substances are accounted for from their creation until their dispensing or destruction. When a controlled substance has become outdated or otherwise unusable, the registrant

who possesses the substance must dispose of it. However, over the past decade, environmental concerns and regulatory changes have caused drug manufacturers and government agencies (including DEA and State authorities) to become increasingly reluctant to be involved in the disposal process. Thus, some disposal options are no longer available." (DEA 2005b)

With this as background to the CSA, the DEA also provides specific answers to two key questions: (1) "Can an individual return their controlled substance prescription medication to a pharmacy?" (DEA 2005c) and (2) "Can a long term care facility (LTCF) return a resident's unused controlled substance medication to a pharmacy?" (DEA 2005d). The answers are: (1) Quoting from DEA (2005c), "An individual patient may not return their unused controlled substance prescription medication to the pharmacy. Federal laws and regulations make no provisions for an individual to return their controlled substance prescription medication to a pharmacy for further dispensing or for disposal. There are no provisions in the Controlled Substances Act or Code of Federal Regulations (CFR) for a DEA registrant (i.e., retail pharmacy) to acquire controlled substances from a non-registrant (i.e. individual patient)." "An individual may dispose of their own controlled substance medication without approval from DEA. Medications should be disposed of in such a manner that does not allow for the controlled substances to be easily retrieved." (2) Quoting from DEA (2005d), "There are no provisions in the Controlled Substances Act for a DEA registrant (i.e., retail pharmacy) to acquire controlled substances from a non-registrant (i.e., resident of a LTCF). Most long term care facilities are not licensed by their respective state to handle controlled substances and therefore are not registered with DEA. Long term care facilities act in a custodial capacity, holding controlled substances that, pursuant to a prescription, have been dispensed to and belong to the resident of the LTCF. Federal laws and regulations make no provisions for controlled substances that have already been dispensed to patients, regardless of the packaging method, to be returned to a pharmacy for further dispensing or disposal."

One of the ways the CSA impacts drug returns programs results from the fact that once a controlled substance is dispensed, the prescription label has no marking or indication that the drug is a controlled substance; such markings (e.g., "CII") are only on the manufacturer's original packaging. This makes it difficult for anyone other than a licensed pharmacist to determine the status of the medication. Consequently, in the absence of any legislated change in labeling standards, for any program designed to accept the return of unwanted drugs, a pharmacist must be present to physically separate controlled from non-controlled medications.

Note that drugs used by consumers are often treated differently than those administered in the same household by a licensed health care provider. Consumer household hazardous waste, including pharmaceuticals, is exempted from RCRA. Unwanted pharmaceuticals are considered waste materials only when declared as wastes. Consumer discharge of drugs to sewerage does not violate water regulations as drug residues are not covered by regulations for water quality. Pharmacies, however, can not dispose of those medications containing ingredients that are considered hazardous under RCRA (e.g., P- or U-listed drugs; see Table 1, page 782, Daughton 2003b; also Smith 2006). A wide spectrum of state laws (many of which have conflicting ramifications with respect to drug disposal) govern the handling and disposition of unused drugs; these are compiled in the database "Current Substance Abuse Legislation" (CESAR 2005).

With all of this as background, there are really only four current options for consumers to dispose of unwanted drugs: (1) discard to sewerage after removing from all packaging, (2) pick-up (of non-controlled substances) by community hazardous waste handler, (3) discarding with municipal trash, and (4) drop off at local sites that host drug take-back events overseen by DEA-exempted law enforcement. The second and fourth options, however, are available only in certain locales.

The second option (disposal with community hazardous waste) is a rather confusing area. Transfer of controlled substances would violate the CSA (although most hazardous waste facilities may not be aware of this). A further complication is the difficulty of expecting the consumer to understand which drugs are controlled substances. Absent any eventual take-back program, drug labeling could be used to provide advice on environmental disposition and possible environmental ramifications of improperly disposed materials. As an example, an "environmental labeling" classification system is being developed in Sweden in a collaborative project between Sweden's Department of the Environment and the Stockholm County Council Pharmaceutical Unit (Wennmalm and Gunnarsson 2005; Wennmalm and Martini 2005). Another example is from the European Medicines Agency (EMEA 2005): "Appropriate disposal of unused pharmaceuticals, e.g. when shelf life is expired, is considered important to reduce the exposure of the environment. In order to enhance environmental protection, it is therefore recommended that – even for medicinal products that do not require special disposal measures - package leaflets (patient information leaflets) should include the following general statement: ' Medicines no longer required should not be disposed of via wastewater or the municipal sewage system'." But note that Europe has the option of returning medications to pharmacies.

Absent any imminent nationwide system for drug returns, and with the growing emphasis of local agencies emphasizing the importance of avoiding disposal to sewerage, the most straightforward solution for most consumers is to dispose of their unwanted medications to domestic trash. But note that trash is usually stored in landfills, which can be considered a form of "pollution postponement" (Daughton 2005). Moreover, the single most important aspect of disposal to trash to keep in mind is that it poses imminent risks for both children and "gleaners" (those who rummage through trash), as well as for domestic, feral, and wild animal scavengers (e.g., coyotes, racoons, bears, dogs). Medications improperly stored or disposed with domestic refuse can be accidentally ingested, especially by infants and children. This is the major impetus behind the recommendations of poison control centers to dispose to sewerage. Disposal to trash can also be limited by obstacles posed by little-recognized transportation rules.

With the potential for future pollution aside, a safe and effective protocol for disposal to trash would surprisingly require considerable explanation, as it would involve attention on the part of the consumer to what would probably prove to be too many details; for example, special attention would need to be devoted to medical patches, some of which still contain very toxic levels of residual drug (e.g., fentanyl). Some of the details required for safe disposal to trash include the following. Medicine containers should have the name of the patient obliterated (but not the name of the medicine — in case a poisoning should later occur). To minimize the chances of others gaining access to the disposed medications, the medicine should be placed in leak-proof, double (nested), opaque containers and tightly sealed (e.g., with heavy-duty packing tape); the containers should not have originally contained food (to discourage their opening by others). This will also prevent casual inspection by others who might then be enticed to consume or sell the medication. To further minimize access by others, the packaged medications should be placed at curb-side as close as possible to the actual time of pick up. One particular note of caution. There has been considerable discussion about the need to render unwanted medications unsuitable for consumption (e.g., by adding reactive chemicals, by heating, or by disassembly of capsules or crushing tablets). Such procedures could be hazardous because they promote the unnecessary handling of active ingredients and can lead to dermal or pulmonary exposure (e.g., by hand contact or inhalation of dusts) or the generation of highly hazardous vapors (e.g., if denaturing chemicals, such as bleach, or heat are used).

Becoming more widely accepted or recognized is the fact that none of these options embodies the dual objectives of protecting human health and safety together with ecological integrity. This is what leads to the need for creating take-back programs, preferably those that are statewide or nationwide in scope.

In 2004, State of Maine legislation enacted the nation's first statewide program for take-back of unused drugs: “An Act to Encourage the Proper Disposal of Unused Pharmaceuticals” (State of Maine 2004). As of early 2006, this program had not yet been implemented, but it would allow individuals to safely dispose of their unused medications by mailing unused pharmaceuticals in a prepaid mailer to the Maine Drug Enforcement Agency for destruction (via incineration). This particular approach would be amenable to templating across the U.S. A summary of recommendations regarding the Maine program is available (State of Maine 2005).

Attention to the need for take-back programs is also developing within medical associations and pharmaceutical organizations. First steps include: (i) a position adopted by the American Society of Consultant Pharmacists (ASCP 2003) where unused non-controlled substances dispensed by long-term care facility pharmacies may be returned to the pharmacy for reuse, (ii) a resolution adopted by the U.S. Pharmacopeia Convention (USP 2005) aimed at working with "appropriate constituencies to continue developing programs to promote safe medication use and disposal," (iii) the May 2005 Assembly of the American Psychiatric Association endorsed a paper encouraging state and federal legislation for programs aimed at the proper disposal of unused pharmaceuticals, and (iv) In April 2006, the National Association of Boards of Pharmacy adopted a resolution to "Develop Legal and Environmentally Safe Programs for the Disposal of Unwanted Medications."

The prospects for future advances in designing more effective take-back programs hinge largely on whether current regulatory practices can be modified, especially with respect to improved means for handling the disposition of controlled substances between non-registrants (e.g., the consumer) and other entities; the most likely target for legislative change would be via modification of 21 CFR part 1307.21 (DEA 1997).

Example of the Hazards Associated with Storage of Drugs at the Home :

The following illustrates the hazards associated with maintaining easy access to multiple medications (prescription and OTC alike) for both children and adults by on-site storage in the home. As an extreme example, even medications formulated specifically for infants can prove toxic when consumed by adults. Consider the case of NSAIDs (non-steroidal anti-inflammatories) and specifically acetaminophen; note that acetaminophen is not an NSAID, as it is not an anti-inflammatory, but it is often loosely lumped under the NSAID category. Every NSAID (like any drug) has a maximum: safe unit dose, cumulative daily dose, and duration of dosing. Safe, recommended doses of any particular NSAID can be easily exceeded even when following prudent/safe-use instructions for the individual product. This situation results from aggregate exposure (ingesting another medication containing the same active ingredient); acetaminophen is used in antihistamines, cough and cold preparations, flu medications, and analgesics. Many individual formulations contain the maximum safe dosage for a particular NSAID. Unwitting toxic cumulative exposure can result from the consumption of multiple formulations of the same drug. Even different formulations from same manufacturer can contain different amounts of the same active ingredient, leading to confusion regarding total amount ingested. For example, different products from a particular, single manufacturer can contain acetaminophen in dosage amounts of 80, 160, 325, 500, 650, or 1,000 milligrams. These dosages are provided in 11 distinct adult formulations and 13 distinct child formulations. If an adult used 2 tablespoons of concentrated drops formulated for infants, the dose (nearly 3 grams) would be toxic; likewise, if a child were to ingest 1 teaspoon, the dose (500 mg) would prove toxic. For NSAIDs in general, the purposeful or inadvertent consumption of excessive aggregate doses from multiple sources results in over 16,000 deaths annually in the U.S. and over 100,000 hospitalizations from NSAID-related complications (Singh 2000). Many of these poisonings result from confusion that derives from the storage of multiple medications.

Similarly, the storage of left-over drugs exacerbates the confusion caused by the well-known problem of similar-looking and similar-sounding medication names. This is another cause of accidental ingestion of incorrect medication. There are more than 15,000 formulary names in the U.S. comprising several thousand distinct drug entities. There are hundreds of instances with similar-looking names (Celebrex vs. Celexa vs. Cerebyx), similar-sounding names (Sarafem vs. Serophene), similar-looking pills (color or shape), and similar-looking packaging (numerous examples can be accessed at the U.S. Pharmacopeia's web site: http://www.usp.org/). The hazards of polypharmacy are increased by any added confusion regarding drug names or drug doses. The hazards of polypharmacy (combined pharmacotherapy, or sometimes called "stacking") result when multiple, distinct drugs are prescribed for different therapeutic endpoints but they all impart the same side effect; a closely related problem is the prescribing of multiple medications (for a patient with undisclosed multiple specialists) that all share the same mode of action for either the therapeutic endpoint or a side-effect (e.g., anticholinergic syndrome or drug-induced delirium in geriatric patients). Different products containing the same API from different manufacturers are available for different intended therapies. Analogous confusion exists when a patient with undisclosed multiple physicians receives prescriptions containing the same drug entity (with different names) but marketed for different disorders. Examples include fluoxetine HCl in form of Sarafem (for PMDD) and Prozac (for depression); and bupropion HCl for depression (Wellbutrin), smoking cessation (Zyban), and anorexia nervosa.

The main point from these examples is that reducing medication storage in the home of medications can reduce the incidence of self-medication and polypharmacy and its attendant hazards that result in part from confusion of the consumer.

DRUG RE-USE and RECYCLING

Another means that consumers sometimes employ for dealing with left-over drugs is the practice of reusing drugs by providing them to another end-user. While not always legal (e.g., for prescription substances) or medically prudent, reuse is usually accomplished by donation to charitable organizations or by sharing with family and friends. Among the available approaches for avoiding disposal or destruction of leftover drugs, is recycling. "Re-cycling" can be distinguished from "re-use" in that the active ingredient from the drug is reclaimed by repurifying either from the original formulation or even from excreted waste. This has been proposed, for example, in the form of "mining" drugs from excreta and other wastes, as noted by Daughton (2003b). An example of such a process has been under development (Pharmaceuticals.org 2005); this is analogous to the reclamation of illicit methamphetamine from the urine of meth users. Perhaps a less confusing term for drug "re-use" would be drug "redistribution" to lessen confusion with drug "recycling," which could be reserved for the re-use of the active ingredient after it has already been used (and excreted).

The most prevalent practices of drug reuse are donation and sharing. The problems associated with charitable drug donations are discussed by Daughton (2003b) and can be substantial. While proper charitable drug contributions can play an essential role in humanitarian relief efforts, inappropriate charitable donations can become a significant source of drugs as environmental pollutants. For example, despite the fact that knowledgeable relief agencies for the 2005 Indonesian tsunami relief efforts attempted to avert the donation of medicines (based on their prior negative experience in Kosovo, where massive quantities of unusable medications had to be disposed at considerable cost), many companies and individuals worldwide ignored the guidelines for donations (Pharmaceutical Journal 2005a). Drug redistribution is also becoming a practice among certain physicians and nursing homes who do not want medications to go unused. Redistribution is targeted to those who cannot afford medical care; for example, recent legislation (see: California 2005) authorizes counties to collect unused prescriptions

from nursing homes, wholesalers, and manufacturers, for redistribution to those having low-income and no medical insurance.

For individuals, relief organizations maintain that it is best to refrain from making donations of medications; monetary donations are usually more useful for relief efforts. The flood of donated medicines that arrive after disasters can create chaos of its own by necessitating that already limited resources be siphoned away from other tasks. The huge quantities of donated drugs need to be stored (often in large warehouses), cataloged, and secured; proper storage conditions for many medicines may not be available or affordable. A large percentage will eventually need to be disposed, and since proper incinerators are scarce, an unknown amount of environmental pollution can result. Significant drug diversion can also result, especially from the inability to sufficiently secure controlled substances and other drugs that can then reenter commercial distribution. Worldwide harmonized guidelines for drug donations are needed to avoid continuing problems with drug donations during relief efforts. Reference resources and guidelines for drug donations are available from WHO (1999), Autier et al. (2002), and from the links provided by the Pharmaceutical Journal (2005b).

In contrast with donations and redistribution, drug "sharing" probably does not play a significant role as an added source of environmental residues, but it does pose substantial acute risks with regard to human health and safety. Drug sharing is a practice that continues to grow as a result of frustration from not being able to make use of drugs that one person no longer wants or needs but which another person does (e.g., Strom 2005). Both consumers and physicians sometimes practice it. Drug sharing, however, is not legal (for prescription medications) and can be hazardous. The practice of self-medication is hazardous itself and is responsible for a large percentage of hospitalizations from adverse drug responses (e.g., wrong drug, wrong dosage). Drug sharing also raises the chances of introduction of counterfeit and expired drugs into the supply chain.

SUMMARY

The sources that contribute residues of human and veterinary drugs to the environment are wide in scope and tend to be diffuse in nature; some point sources for acute levels, however, are known to exist and can cause environmental damage. Although parallels exist between the origins of human drugs and those designed for animals, there are some distinct differences as well, which lead to different exposure scenarios for non-target wildlife. A vast array of approaches exist, or could be developed, for reducing these sources and thereby lessening environmental loads of PPCP residues. All sources hold the potential for control or reduction of their releases to the environment, but the associated costs and other ramifications for implementing some of these approaches could be great. Perhaps the major overlooked benefit of PPCP pollution reduction is the potential it holds for collateral improvements in the administration of health care, reducing health care costs, in improving therapeutic outcomes, and in lessening the consumer-acceptance problems associated with risk perception and recycled wastewater.

NOTICE

The US Environmental Protection Agency (EPA), through its Office of Research and Development (ORD), funded and performed the research described. This manuscript has been subjected to the EPA's peer and administrative review and has been approved for publication.

REFERENCES CITED:

[Note regarding URLs: References in this paper rely extensively on Internet URLs (Universal Resource Locators), which can cease to function for any number of reasons. To locate information on web pages no longer accessible, an archive service such as the "Internet Archive Wayback Machine"

(http://www.archive.org) can be useful. Other information regarding non-functional URLs can be located at: http://epa.gov/nerlesd1/chemistry/ppcp/advice.htm ("Advice on Non-Functional URLs").]

AAPCC "Toxic Exposure Surveillance System," American Association of Poison Control Centers, web page 2005; available: TESS: http://www.aapcc.org/poison1.htm

D. A Alvarez, J. D. Petty, J. N. Huckins, T. Jones-Lepp, D. T. Getting and S. E. Manahan "Development of a Passive, In Situ, Integrative Sampler For Hydrophillic Organic Contaminants In Aquatic Environments," Environ. Toxicol. Chem., 23(7) (2004) 1640-1648.

ASCP "Statement on the Return and Reuse of Medications in Long-term Care Facilities," American Society of Consultant Pharmacists, Board of Directors, 11 July 2003; available: . http://www.ascp.com/public/pr/policy/return.shtml

ASPCA "Animal Poison Control Center," American Society for the Prevention of Cruelty to Animals web page 2005; available: http://www.apcc.aspca.org

M. Auriol, Y. Filali-Meknassi, R.D. Tyagi, C.D. Adams, and R.Y. Surampalli "Endocrine disrupting compounds removal from wastewater, a new challenge," Process Biochem., 41(3) (2006) 525-539.

P. Autier, R. Govindaraj, R. Gray, R. Lakshminarayanan, H.G. Nassery, and G. Schmets "Drug Donations in Post-emergency Situations," Health, Nutrition and Population (HNP) Discussion Paper (Ed. Alexander S. Preker), 2002, The International Bank for Reconstruction and Development, The World Bank, Washington, DC, ISBN 1-932126-18-X; available: http://www-wds.worldbank.org/servlet/WDS_IBank_Servlet?pcont=details&eid=000160016_20040513164737

M.E. Balmer, H.-R. Buser, M.D. Muller, T. Poiger "Occurrence of Some Organic UV Filters in Wastewater, in Surface Waters, and in Fish from Swiss Lakes," Environ. Sci. Technol., 39(4) (2005) 953-962.

D. Bendz, N.A. Paxéus, T.R. Ginn, and F.J. Loge "Occurrence and fate of pharmaceutically active compounds in the environment, a case study: Höje River in Sweden," J. Hazard. Materials, 122(3) (2005) 195-204.

P. Berckmans, V. Dawans, G. Schmets, D. Vandenbergh and P. Autier "Inappropriate Drug-Donation Practices in Bosnia and Herzegovina, 1992 to 1996," New Eng. J. Med., 337(25) (1997) 1842-1845.

BNF "British National Formulary 50," September 2005, BMJ Publishing Group Ltd and Royal Pharmaceutical Society of Great Britain; available (login required): http://www.bnf.org/bnf/bnf/current/noframes/index.htm

J.P. Bound, K. Kitsou and N. Voulvoulis "Household disposal of pharmaceuticals and perception of risk to the environment," Environ. Toxicol. Pharmacol., 21(3) (2006) 301-307..

J. P. Bound and N. Voulvoulis "Household Disposal of Pharmaceuticals as a Pathway for Aquatic Contamination in the United Kingdom," Environ. Health Perspect., 113(12) (2005) 1705-1711.

A.B. Boxall, L.A. Fogg, P.A. Blackwell, P. Kay, E.J. Pemberton, and A. Croxford "Veterinary Medicines in the Environment," Rev. Environ. Contam. Toxicol., 180 (2004) 1-91.

A.B.A. Boxall, P. Johnson, E.J. Smith, C.J. Sinclair, E. Stutt, and L.S. Levy "Uptake of Veterinary Medicines from Soils into Plants," J. Agric. Food Chem., 54(6) (2006) 2288-2297.

H. Breton, M. Cociglio, F. Bressolle, H. Peyriere, J.P. Blayac, and D. Hillaire-Buys "Liquid chromatography–electrospray mass spectrometry determination of carbamazepine, oxcarbazepine and eight of their metabolites in human plasma," J Chromatogr B, 828(1-2) (2005) 80-90.

H.-R. Buser, M.E. Balmer, P. Schmid, M, Kohler "Occurrence of UV Filters 4-Methylbenzylidene Camphor and Octocrylene in Fish from Various Swiss Rivers with Inputs from Wastewater Treatment Plants," Environ. Sci. Technol., 40(5) (2006) 1427-1431.

California "SB 798, Simitian. Prescription Drugs: Collection and Distribution Program," Senate Bill No. 798, State of California, 14 September 2005; available: http://www.leginfo.ca.gov/pub/bill/sen/sb_0751-0800/sb_798_bill_20050913_enrolled.pdf

A.C. Capleton, C. Courage, P. Rumsby, P. Holmes, E. Stutt, A.B.A. Boxall, and L.S. Levy "Prioritising veterinary medicines according to their potential indirect human exposure and toxicity profile," Toxicol. Lett., 163(3) (2006) 213-223.

CARB "Consumer products program," web page 2005, California Air Resources Board, Sacramento, CA; available: http://www.arb.ca.gov/consprod/consprod.htm.

CESAR "Current Substance Abuse Legislation," Center for Substance Abuse Research, CESAR, University of Maryland, web page 2005; available: http://www.cesar.umd.edu/cesar/library/statutes.asp

C.G. Daughton "Illicit Drugs in Municipal Sewage: Proposed New Non-Intrusive Tool to Heighten Public Awareness of Societal Use of Illicit/Abused Drugs and Their Potential for Ecological Consequences," in C.G. Daughton and T.L. Jones-Lepp (Editors), Pharmaceuticals and Personal Care Products in the Environment: Scientific and Regulatory Issues, Symposium Series 791, American Chemical Society: Washington, D.C., 2001, pp. 348-364; available: http://epa.gov/nerlesd1/chemistry/pharma/book-conclude.htm.

C.G. Daughton "Environmental stewardship and drugs as pollutants," Lancet**,** 360 (2002) 1035-1036; available: http://epa.gov/nerlesd1/chemistry/pharma/images/lancet-final.pdf.

C.G. Daughton "Cradle-to-Cradle Stewardship of Drugs for Minimizing Their Environmental Disposition while Promoting Human Health. I. Rationale for and Avenues toward a Green Pharmacy," Environ. Health Perspect., 111 (2003a) 757-774; available: http://www.epa.gov/nerlesd1/chemistry/ppcp/images/green1.pdf.

C.G. Daughton "Cradle-to-Cradle Stewardship of Drugs for Minimizing Their Environmental Disposition while Promoting Human Health. II. Drug Disposal, Waste Reduction, and Future Direction," Environ. Health Perspect., 111 (2003b) 775-785; available: http://www.epa.gov/nerlesd1/chemistry/ppcp/images/green2.pdf.

C.G. Daughton "Environmental Stewardship of Pharmaceuticals: The Green Pharmacy," In the Proceedings of the 3rd International Conference on Pharmaceuticals and Endocrine Disrupting Chemicals in Water, National Ground Water Association, 19-21 March 2003c, Minneapolis, MN; available: http://www.epa.gov/nerlesd1/chemistry/ppcp/images/ngwa2003.pdf.

C.G. Daughton "Groundwater Recharge and Chemical Contaminants: Challenges in Communicating the Connections and Collisions of Two Disparate Worlds," Ground Water Monitor. Remed., 24(2) (2004a) 127-138 ; available: http://www.epa.gov/nerlesd1/chemistry/ppcp/images/water-reuse.pdf

C.G. Daughton "Non-Regulated Water Contaminants: Emerging Research," Environ. Impact Assess. Rev., 24(7-8) (2004b) 711-732; available: http://epa.gov/nerlesd1/chemistry/pharma/images/EIAR.pdf

C.G. Daughton "PPCPs in the Environment: Future Research — Beginning with the End Always in Mind," In Pharmaceuticals in the Environment, Kümmerer, K. (Ed.), 2nd edition, Springer, 2004c, Chapter 33, pp. 463-495; available: http://epa.gov/nerlesd1/chemistry/ppcp/images/researchneeds-chapter.pdf

C.G. Daughton " 'Emerging' Chemicals as Pollutants in the Environment: a 21st Century Perspective," Renewable Resources J., 23(4) (2005) 6-23.

Daughton/EPA "References Relevant to PPCPs in the Environment," US Environmental Protection Agency, Las Vegas, NV, web page 2005; available: http://www.epa.gov/nerlesd1/chemistry/ppcp/reference.htm

C.G. Daughton T.L. Jones-Lepp (Editors) Pharmaceuticals and Personal Care Products in the Environment: Scientific and Regulatory Issues, *Symposium Series 791*; American Chemical Society: Washington, D.C., 2001, 416 pp; available: http://epa.gov/nerlesd1/chemistry/pharma/book.htm

C.G. Daughton T.A. Ternes "Pharmaceuticals and Personal Care Products in the Environment: Agents of Subtle Change?" Environ. Health Perspect. 107(suppl 6) (1999) 907-938; available: http://epa.gov/nerlesd1/chemistry/ppcp/images/errata.pdf.

DEA "Disposal of Controlled Substances, Section 1307.21 Procedure for disposing of controlled substances," 21 CFR part 1307.21, Federal Register; 24 March 1997; available: http://www.deadiversion.usdoj.gov/21cfr/cfr/1307/1307_21.htm

DEA "Controlled Substances Act," U.S. Drug Enforcement Adminstration, web page 2005a; available: http://www.usdoj.gov/dea/agency/csa.htm

DEA "Definition and Registration of Reverse Distributors," 21 CFR Parts 1300, 1301, 1304, 1305, and 1307, Federal Register, 2 May 2005b, 70(83):22591-22595; available: (http://edocket.access.gpo.gov/2005/05-8692.htm

DEA "Can an individual return their controlled substance prescription medication to a pharmacy?" General Questions & Answers (web page), Office of Diversion Control, Drug Enforcement Administration, 2005c; available: http://www.deadiversion.usdoj.gov/faq/general.htm#pre_med

DEA "Can a long term care facility (LTCF) return a resident's unused controlled substance medication to a pharmacy?" General Questions & Answers (web page), Office of Diversion Control, Drug Enforcement Administration, 2005d; available: http://www.deadiversion.usdoj.gov/faq/general.htm#ltcf

M.S. Díaz-Cruz, M.J. López de Alda, and Damià Barceló "Environmental Behavior and Analysis of Veterinary and Human Drugs in Soils, Sediments and Sludge," TrAC Trends Anal. Chem., 22(6) (2003) 340-351.

DOHMH "NYC Health Dept. Warns Against Use of 'Skin-lightening' Creams Containing Mercury or Similar Products Which Do Not List Ingredients," New York City Department of Health and Mental Hygiene, New York, press release 27 January 2005; available: http://www.nyc.gov/html/doh/html/pr/pr008-05.shtml

J. Drews "Drug Discovery: A Historical Perspective," Science, 287(5460) (2000) 1960-1964.

EBRx "Preferred Drug List," 1 January 2006, Columbus, OH; available: http://www.ebrx.com/Docs/EBRxPreferredFormulary.pdf

EMEA "Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use," Committee for Medicinal Products for Human Use (CHMP), Pre-Authorisation Evaluation of Medicines for Human Use, London, UK, 20 January 2005, CHMP/SWP/4447/00 draft (page 14, section 6: 6. Precautionary and Safety Measures to Be Taken for Administration, Disposal and Labelling); available: http://www.emea.eu.int/pdfs/human/swp/444700en.pdf

EPA "Profile of the Pharmaceutical Manufacturing Industry," Office of Compliance Sector Notebook Project, EPA/310-R-97-005, Office of Compliance, Office of Enforcement and Compliance Assurance, U.S. Environmental Protection Agency, September 1997; available: http://www.epa.gov/compliance/resources/publications/assistance/sectors/notebooks/pharma.pdf

EPA "Development Document for Final Effluent Limitations Guidelines and Standards for the Pharmaceutical Manufacturing Point Source Category," Office of Water, U.S. Environmental Protection Agency, EPA-921-R-98-005, September 1998; available: http://epa.gov/ostwater/guide/pharm/techdev.html

EPA "General Information on Concentrated Animal Feeding Operations," U.S. Environmental Protection Agency, web page, 20 October 2004a; available: http://cfpub.epa.gov/npdes/afo/info.cfm

EPA "Environmental Impacts from Aquaculture Facilities," Chapter 7 (available: http://epa.gov/guide/aquaculture/EEBA/EEBA%20-%20Chapter%207.pdf), in "Economic and Environmental Benefits Analysis of the Final Effluent Limitations Guidelines and New Source Performance Standards for the Concentrated Aquatic Animal Production Industry Point Source Category," U.S. Environmental Protection Agency, Washington, D.C., EPA-821-R-04-013, June 2004b (available: http://epa.gov/guide/aquaculture/EEBA/index.html).

EPA "Everyday Choices: Opportunities for Environmental Stewardship," Technical Report prepared by the U.S. EPA Environmental Stewardship Staff Committee for the EPA Innovation Action Council, November 2005, 100 pp.; available: http://www.epa.gov/innovation/pdf/techrpt.pdf

EPA "Permit Guidance Document: Pharmaceutical Manufacturing Point Source Category," 40 CFR Part 439, Office of Water, U.S. Environmental Protection Agency, Washington, D.C., January 2006a, EPA 821-F-05-006; available: http://www.epa.gov/waterscience/guide/pharm/guidance/pharmaceuticals-guidance.pdf

EPA "Aquatic Animal Production Industry Effluent Guidelines," web page, U.S. Environmental Protection Agency, Washington, D.C., 2006b; available: http://epa.gov/guide/aquaculture/#rule

E. Eriksson, K. Auffarth, A-M. Eilersen, M. Henze and A. Ledin "Household chemicals and personal care products as sources for xenobiotic organic compounds in grey wastewater," Water SA, 29(2) (2003) 135-146; available: http://www.wrc.org.za/archives/watersa%20archive/2003/april/4.pdf

EWG "Skin Deep: A Safety Assessment of Ingredients in Personal Care Products," Environmental Working Group, Washington, DC, June 2004; available: http://www.ewg.org/reports/skindeep/

FAO "The State of World Fisheries and Aquaculture: Part 2. Selected Issues Facing Fishers and Aquaculture (Antibiotic Residues in Aquaculture Products)," Food and Agriculture Organization of the United Nations, FAO Fisheries Department, 2002; available: http://www.fao.org/documents/show_cdr.asp?url_file=//docrep/005/y7300e/y7300e00.htm

FDA "Environmental Warning Added to Animal Euthanasia Products," Center for Veterinary Medicine, U.S. Food and Drug Administration, 22 July 2003; available: http://www.fda.gov/cvm/CVM_Updates/wildup_com.htm

FDA "Approved Drug Products with Therapeutic Equivalence Evaluations: Orange Book," Center for Drug Evaluation and Research, U.S. Food and Drug Administration, 2005a (web page); available: http://www.fda.gov/cder/orange/default.htm

FDA "Approved Drug Products with Therapeutic Equivalence Evaluations," 25th Edition, Cumulative Supplement 3, Office of Pharmaceutical Science, Office of Generic Drugs, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, March 2005b; available: http://www.fda.gov/cder/orange/supplement/cspreface.htm

FDA "CDER Approval Times for Priority and Standard NMEs and New BLAs Calendar Years 1993 - 2004," Center for Drug Evaluation and Research, U.S. Food and Drug Administration, 2005c (web page); available: http://www.fda.gov/CDER/rdmt/NMEapps93-04.htm

FDA "Approved Animal Drug Products: Green Book," Drug Information Laboratory, Center for Veterinary Medicine, U.S. Food and Drug Administration, 2005d; available: http://www.fda.gov/cvm/Green_Book/greenbook.html

FDA "Environmental Assessments, Findings of No Significant Impact, and Environmental Impact Statements," web page, Center for Veterinary Medicine, U.S. Food and Drug Administration, 2006; available: http://www.fda.gov/cvm/ea.htm

K. Fent, A.A. Weston and D. Caminada "Ecotoxicology of human pharmaceuticals," Aquatic Toxicol., 76(2) (2006) 122-159.

P.M.J Fisher and R. Borland "Gauging the Pharmaceutical Burden on Sydney's Environment: a Preventative Response," J. Cleaner Prod., 11 (2003) 315-320.

L.J. Fono and D.L. Sedlak "Use of the Chiral Pharmaceutical Propranolol to Identify Sewage Discharges into Surface Waters," Environ. Sci. Technol., 39(23), (2005) 9244-9252.

B. Halling-Sørensen B, S.N. Nielsen, P.F, Lanzky, F. Ingerslev, H.C.H. Lutzhoft, S.E. Jorgensen "Occurrence, Fate and Effects of Pharmaceutical Substances in the Environment—a Review," Chemosphere 36(2) (1998) 357–393.

G. Hamscher, H.T. Pawelzick, S. Sczensky, H. Nau and J. Hartung."Antibiotics in dust originating from a pig-fattening farm: A new source of health hazard for farmers?" Environ. Health Perspect. 111(13) (2003) 1590-1594.

M. Harada, S. Nakachi, K. Tasaka, S. Sakashita, K. Muta, K. Yanagida, R. Doi, T. Kizaki and H. Ohno "Wide use of skin-lightening soap may cause mercury poisoning in Kenya," Sci. Total Environ., 269(1-3) (2001) 183-187.

P. Harremoës, D. Gee, M. MacGarvin, A. Stirling, J. Keys, B. Wynne B, et al., eds. 2001. Late Lessons from Early Warnings: The Precautionary Principle 1896–2000. Environmental issue report no. 22. Copenhagen, Office for Official Publications of the European Communities; available: http://reports.eea.eu.int/environmental_issue_report_2001_22/en

T. Heberer "Occurrence, Fate, and Removal of Pharmaceutical Residues in the Aquatic Environment: a Review of Recent Research Data," Toxicol. Lett., 131(1-2) (2002) 5-17.

HHS "Health, United States, 2004: 28th Report on the Health Status of the Nation," Department of Health and Human Services, September 2004, DHHS Publication number 2004-1232; available: http://www.cdc.gov/nchs/data/hus/hus04.pdf

B. Hileman "Counterfeit Drugs," Chem. Eng. News, 81(45) (2003) 36-43; available: http://pubs.acs.org/cen/coverstory/8145/8145drugs.html

IMS Health "IMS Health Reports 5.4 Percent Dollar Growth in 2005 U.S. Prescription Sales," IMS Health Incorporated, press release, 22 February 2006; available: http://www.imshealth.com/ims/portal/front/articleC/0,2777,6599_3665_77180090,00.html

IMS Health "Looking to China and Cancer As Cost Containment Slows Growth," IMS Health Incorporated, web page 2005; available: http://www.imshealth.com/web/content/0,3148,64576068_63872702_70260998_73052844,00.html

R.G. Hollingsworth, J.W. Armstrong, and E. Campbell "Pest Control: Caffeine as a Repellent for Slugs and Snails," Nature 417 (2002) 915-916.

IPEC, web home page, International Pharmaceutical Excipients Council, Trade Association of Manufacturers and Users of Pharmaceutical Excipients, 2006; available: http://www.ipec.org/

P.K. Jjemba "The potential impact of veterinary and human therapeutic agents in manure and biosolids on plants grown on arable land: a review," Agric. Ecosys. Environ., 93(1-3) (2002) 267-278.

S.E. Jorgensen and B. Halling-Sørensen "Drugs in the Environment," Chemosphere 40(7) (2000) 691-699.

C.A. Kenreigh and L.T. Wagner "Medication Adherence: A Literature Review," Medscape Pharmacists, 6(2) (2005); available: http://www.medscape.com/viewarticle/514164_print

S.J. Khan and L.E. Gerrard "Stakeholder communications for successful water reuse operations," Desalination, 187(1-3) (2006) 191-202; available: http://www.desline.com/articoli/6969.pdf

C.A. Kinney, E.T. Furlong, S.L. Werner, and J.D. Cahill "Presence and distribution of wastewater-derived pharmaceuticals in soil irrigated with reclaimed water," Environ. Toxicol. Chem., 25(2) (2006) 317-326.

D.W. Kolpin, E.T. Furlong, M.T. Meyer, E.M Thurman, S.D. Zaugg, L.B. Barber, and H.T. Buxton "Pharmaceuticals, Hormones, and Other Organic Wastewater Contaminants in U.S. Streams, 1999-2000: a National Reconnaissance," Environ. Sci. Technol. 36(6) (2002) 1202-1211.

K. Kümmerer "Drugs in the Environment: Emission of Drugs, Diagnostic Aids and Disinfectants into Wastewater by Hospitals in Relation to Other Sources - a Review," Chemosphere 45(6-7) (2001) 957-969

K. Kümmerer (Ed.), Pharmaceuticals in the Environment: Sources, Fate, Effects and Risks, 2nd ed., Springer, Germany, 2004.

L. Lissemore, C. Hao, P. Yang, P.K. Sibley, S. Mabury, and K.R. Solomon "An exposure assessment for selected pharmaceuticals within a watershed in Southern Ontario," Chemosphere, in press (2006); available online 5 January 2006.

W. McDonough and M. Braungart Cradle to Cradle: Remaking the Way We Make Things, North Point Press, April 2002; available: http://www.mbdc.com/book/index.htm.

Med Ad News "Top 500 Prescription Drugs," PharmaLive.com Special Report, Med Ad News, May 2005; available: http://www.pharmalive.com/special_reports/sample.cfm?reportID=191

Medicare "Formulary Finder for Prescription Drug Plans," web page, Centers for Medicare & Medicaid Services, U.S. Department of Health and Human Services, 2006; available: http://www.medicare.gov/MPDPF/Shared/Include/Formulary/FormularyFinder.asp

X.-S. Miao and C.D. Metcalfe "Determination of carbamazepine and its metabolites in aqueous samples using liquid chromatography-electrospray tandem mass spectrometry," Anal. Chem., 75(15) (2003) 3731-3738.

M.H.M.M. Montforts "The Trigger Values in the Environmental Risk Assessment for (Veterinary) Medicines in the European Union: a Critical Appraisal," RIVM report 601500002/2005, Expert Centre for Substances of the RIVM, National Institute for Public Health and the Environment (RIVM), Netherlands, 45 pp., 2005a; available: http://www.rivm.nl/bibliotheek/rapporten/601500002.pdf

M.H.M.M. Montforts "Validation of the EU Environmental Risk Assessment for Veterinary Medicines," Doctoral Thesis, Leiden University 20 April 2005b; available: http://openaccess.leidenuniv.nl/dspace/bitstream/1887/648/1/thesis+montforts.pdf

NDCHealth "NDC Pharmaceutical Audit Suite (PHAST)," NDCHealth, Atlanta, GA, 2005a; available: http://www.ndchealth.com/pharmaceutical/ndc_phast.htm (see: http://www.rxlist.com/top200.htm).

NDCHealth "NDC Pharmaceutical Audit Suite (PHAST)," NDCHealth, Atlanta, GA, 2005b; available: http://www.ndchealth.com/pharmaceutical/ndc_phast.htm (see: http://www.rxlist.com/top200_sales_2004.htm).

C. Nemeroff and P. Rozin "The Contagion Concept in Adult Thinking in the United States: Transmission of Germs and of Interpersonal Influence," Ethos 22(2) (1994) 158-186.

NERC "Report on In-store Pilot CVS Mill Creek, South Portland, Maine, Saturday, February 5, 2005, 9–5," Northeast Recycling Council, Inc., Brattleboro, VT, 2005; available: http://www.nerc.org/adobe/CVSPilotReportFINAL.pdf

J.L. Oaks, M. Gilbert, M.Z. Virani, R.T. Watson, C.U. Meteyer, B.A. Rideout, H.L Shivaprasad, S. Ahmed, M.J.I. Chaudhry, M. Arshad, S. Mahmood, A. Ali and A.A. Khan "Diclofenac residues as the cause of vulture population decline in Pakistan," Nature, 427 (2004) 630-633.

ONDCP "Prescription Drug Abuse: A Dangerous Trend Among Teens," White House Office of National Drug Control Policy, National Youth Anti-Drug Media Campaign, web page 2005; available: http://www.theantidrug.com/drug_info/prescription_news.asp

Oregon DHS "Lead Found in Traditional Home Remedies," Lead Poisoning Prevention Program, web page 2005, Oregon Department of Human Services (DHS), Office of Environmental and Occupational Epidemiology (EOE), Oregon; available: http://www.dhs.state.or.us/publichealth/lead/homerx.cfm

L. Osterberg and T. Blaschke "Adherence to Medication," New Eng. J. Med., 353(5) (2005) 487-497; available: http://content.nejm.org/cgi/content/full/353/5/487?ijkey=3daX237PepUF6&keytype=ref&siteid=nejm

J.A. Pedersen, M.A. Yeager and I.H. Suffet "Xenobiotic Organic Compounds in Runoff from Fields Irrigated with Treated Wastewater," J. Agric. Food Chem., 51(5) (2003) 1360-1372.

M. Petrovic, M.D. Hernando, M.S. Díaz-Cruz, and D. Barceló "Liquid Chromatography–tandem Mass Spectrometry for the Analysis of Pharmaceutical Residues in Environmental Samples: a Review," J. Chromatogr. A, 1067(1-2) (2005) 1-14.

Pharmaceutical Journal "Tonnes of inappropriate medicines arrive in SE Asia," The Pharmaceutical Journal, 2005a, 274(7335):139; available: http://www.pharmj.com/Editorial/20050205/news/p139asia.html

Pharmaceutical Journal "Charitable Requests & Volunteers: Drug Donations," Pharmaceutical Journal online, 2005b web page; available: http://www.pharmj.com/makingadifference/index.html

Pharmaceuticals.org. "Pharmaceuticals from Human System to the Human System," Utica, MI, Pharmaceuticals.org, Inc., web page 2005; available: http://www.toilets.com/pharmaceuticals.htm

M. Poliakoff, J.M. Fitzpatrick, T.R. Farren, P.T. Anastas, "Green Chemistry: Science and Politics of Change," Science, 297(5582), (2002) 807-810.

K. Rahn "Expired Drugs Headache for Pharmacies," The Korea Times, 1 May 2006

P. Rozin and C.J. Nemeroff"The laws of sympathetic magic: A psychological analysis of similarity and contagion," in J. Stigler, G. Herdt, and R.A. Shweder (Editors), Cultural Psychology: Essays on comparative human development, Cambridge, England, 1990, pp. 205-232.

Rote Liste Service (Ed.) "Rote Liste 2005: Drug directory for Germany including EU-approved drug products and some medical devices," ISBN 3-87193-306-6, 2138 pages, published by ECV - Editio Cantor Verlag.

R.B. Saper, S.N. Kales, J.Paquin, M.J. Burns, D.M. Eisenberg, R.B. Davis and R.S. Phillips, "Heavy Metal Content of Ayurvedic Herbal Medicine Products," J. Am. Med. Assoc., 292 (2004) 2868-2873.

R.J. Savarie, J.S. Shivik, G.C. White, J.C. Hurley, and L. Clark. "Use of Acetaminophen for Large-scale Control of Brown Treesnakes," J. Wildlife Manage. 65 (2001) 356-365; available: http://www.aphis.usda.gov/ws/nwrc/is/01pubs/01-68.pdf

D.L. Sedlak and L. Fono "Use of metoprolol enantiomers to discriminate between combined sewer overflows and wastewater effluent discharges," First Integral Virtual Symposium sponsored by the American Chemical Society [ACS] Division of Environmental Chemistry and the U.S. EPA, ACS 228th National Meeting in Philadelphia, PA, 25-26 August 2004 (http://www.epa.gov/esd/chemistry/ppcp/acs-25aug2004.htm; http://www.envirofacs.org/PPCP2.pdf).

Sedlak, D.L.; Gray, J.L.; Pinkston, K.E. "Understanding micro contaminants in recycled water," Environ. Sci. Technol. 34(23), (2000) 509A-515A.

J.T. Sherer "Pharmaceuticals in the Environment," Am. J. Health Syst. Pharm. 63 (2006) 174-178.

G. Singh "Gastrointestinal Complications of Prescription and Over-the-Counter Nonsteroidal Anti-Inflammatory Drugs: A View from the ARAMIS Database," Am. J. Therapeut., 7 (2000) 115-121.

C.A. Smith "Managing Pharmaceutical Waste: The Role of ICP," Infection Control Resource, Prevention Strategies for IC Practitioners and Professional Nurses, 3(4) (2006) 2-5; available: http://www.infectioncontrolresource.org/Past_Issues/IC12.pdf

State of Maine "An Act To Encourage the Proper Disposal of Expired Pharmaceuticals," Unused Pharmaceutical Disposal Program, State of Maine Legislature LD 1826 (S.P. 671), 121st Maine Legislature, referred to Maine's Committee on Health and Human Services on 8 January 2004; available: http://janus.state.me.us/legis/LawMakerWeb/summary.asp?ID=280012218

State of Maine "Final Report of the Maine Drug Return Implementation Group," State of Maine 122nd Legislature First Regular Session, 8 March 2005; available: http://mainegov-images.informe.org/legis/opla/drugrpt.pdf

S. Strom "Old Pills Finding New Medicine Cabinets," New York Times, 18 May 2005; available: http://www.nytimes.com/2005/05/18/health/18reuse.html)

J.P. Sumpter and A.C. Johnson "Lessons from endocrine disruption and their application to other issues concerning trace organics in the aquatic environment," Environ. Sci. Technol. 39 (2005) 4321-4332.

J.M. Surian "Important Principles in the Design of Oral Immediate and Controlled Release Pharmaceutical Formulations," Am. Pharmaceut. Rev., 9(1) (2006) 35-39; available: http://www.americanpharmaceuticalreview.com/article.aspx?article=368

Z. Takáts, J.M. Wiseman, B. Gologan, R.G. Cooks "Mass Spectrometry Sampling Under Ambient Conditions with Desorption Electrospray Ionization," Science, 306(5695) (2004) 471-473.

T.A. Ternes "Analytical methods for the determination of pharmaceuticals in aqueous environmental samples," TrAC Trends Anal. Chem., 20(8) (2001) 419-434.

A. Tropsha "Recent trends in computer-aided drug discovery," Curr. Opinion Drug Disc. Develop. 3 (2000) 310-313; available: http://www.biomedcentral.com/1367-6733/3?issue=3

B. Turque "Sewage Tested for Signs of Cocaine: Fairfax Participating In Federal Program To Assess Drug Use," Washington Post, 27 March 2006, page B01; available: http://www.washingtonpost.com/wp-dyn/content/article/2006/03/26/AR2006032600880.html

C. Ukens "Staying The Course: New gee-whiz technologies are improving patients' compliance with their drug regimens," Drug Topics, 12 September 2005; available: http://www.drugtopics.com/drugtopics/article/articleDetail.jsp?id=179333

UM "Veterinary Formulary," University of Minnesota, 2006; available: http://www.ahc.umn.edu/rar/umnuser/formulary.html

USDA "Caribbean Tree Frogs in Hawaii," web page, Animal and Plant Health Inspection Service, United States Department of Agriculture, January 2003; available: http://www.aphis.usda.gov/lpa/pubs/pa_wscoquitfrogs.html

USP "Resolution 9: Promoting Safe Medication Use and Disposal," U.S. Pharmacopeia, 2005–2010 Resolutions, adopted at the USP Convention 2005, 13 March 2005; available: http://www.usp.org/aboutUSP/resolutions.html

VFA "The Pharmaceutical Market," Association of Research-based Pharmaceutical Companies (VFA), web page 2005; available: http://www.vfa.de/en/statistics/pharmaceuticalmarket

A. Wennmalm and B. Gunnarsson "Public health care management of water pollution with pharmaceuticals: Environmental classification and analysis of pharmaceutical residues in sewage water," Drug Inform. J., 39(3) (2005) 291-297.

A. Wennmalm and S. Martini "Environment and Pharmaceuticals," Department of the Environment (Sweden) and the Stockholm County Council Pharmaceutical Unit, web page 2005; available: http://www.janusinfo.se/imcms/servlet/GetDoc?meta_id=7236

WHO "General Guidelines for Drug Donations," Department of Essential Drugs and Other Medicines, World Health Organization, Geneva, Switzerland, WHO/EDM/PAR/99.4, Second edition 1999; available: http://www.who.int/hac/techguidance/tools/5.6%20guidelines%20for%20drug%20donations.pdf

E. Zuccato, D. Calamari, M. Natangelo, R. Fanelli, "Presence of therapeutic drugs in the environment," The Lancet, 355 (2000) 1789-1790.

E. Zuccato, C. Chiabrando, S. Castiglioni, D. Calamari, R. Bagnati, S. Schiarea and R. Fanelli "Cocaine in surface waters: a new evidence-based tool to monitor community drug abuse," Environ. Health: A Global Access Science Source, 4(14) (2005), 7 pp.

FIGURE 1. Origins and Fate of PPCPs in the Environment

Copy of figure currently available here:
http://www.epa.gov/ppcp/pdf/drawing.pdf